Appendix D – Breast Cancer Research

Contents

Breast cancer screening cannot be justified, says researcher

Book argues harm outweighs small number of lives saved, and accuses mammography supporters of misconduct

Sarah Boseley, health editor

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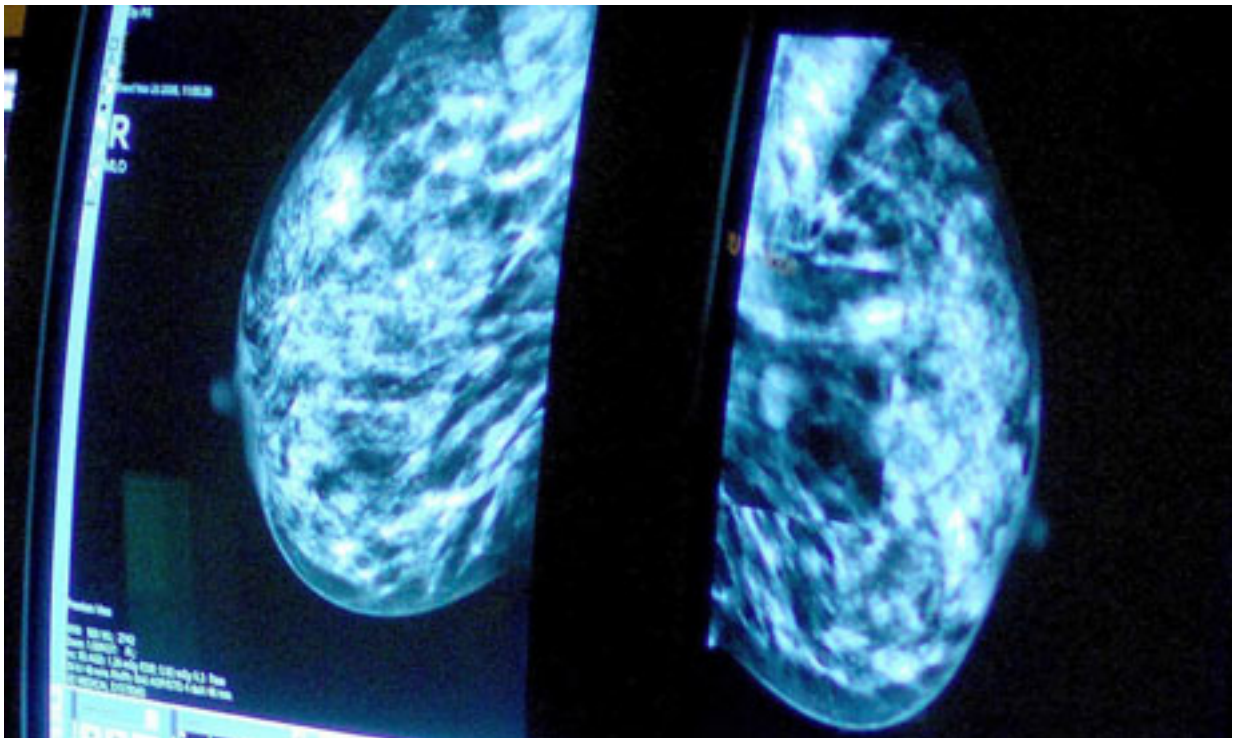
Women in the UK are called for breast screening every three years from the age of 50. Photograph: Rui Vieira/PA

Breast cancer screening can no longer be justified, because the harm to many women from needless diagnosis and damaging treatment outweighs the small number of lives saved, according to a book that accuses many in the scientific establishment of misconduct in their efforts to bury the evidence of critics and keep mammography alive.

Peter Gøtzsche, director of the independent Nordic Cochrane Collaboration, has spent more than 10 years investigating and analysing data from the trials of breast screening that were run, mostly in Sweden, before countries such as the UK introduced their national programmes.

[Mammography screening: truth, lies and controversy](#), from Radcliffe Publishing, spells out the findings of the Nordic Cochrane group for laywomen, rather than for scientists.

The data, Gøtzsche has maintained for more than a decade, does not support mass screening as a preventive measure. Screening does not cut breast [cancer](#) deaths by 30%, it saves probably one life for every 2,000 women who go for a mammogram. But it harms 10 others. Cancerous cells that will go away again or never progress to disease in the woman's lifetime are excised with surgery and sometimes (six times in 10) she will lose a breast. Treatment with radiotherapy and drugs, as well as the surgery itself, all have a heavy mental and physical cost.

"I believe the time has come to realise that breast cancer screening programmes can no longer be justified," Gøtzsche said. "I recommend women to do nothing apart from attending a doctor if they notice anything themselves."

The book is published as a UK review of the evidence for breast cancer screening, triggered by the Nordic Cochrane group's publications in scientific journals, gets under way. In October, the cancer tsar Sir Mike Richards promised an independent [investigation of the data](#). It will be chaired by Sir Michael Marmot and will include some eminent statisticians, none of whom have been involved in the breast screening controversy before.

Richards has promised to act on its findings. "Should the independent review conclude that the balance of harms outweighs the benefits of breast screening, I will have no hesitation in referring the findings to the UK national screening committee and then ministers," he wrote at the time.

Women in the UK are called for breast screening every three years from the age of 50, and the age range is being extended to encompass all from 47 to 73. The [NHS screening programme](#) has consistently disputed the Nordic Cochrane Collaboration's work.

In July last year, in response to a paper that showed no difference in death rates between similar pairs of countries that had introduced or not introduced screening, Professor Julietta Patnick, director of the NHS cancer screening programmes, said: "We can't comment on screening programmes in other countries but here in England we do know that the best evidence available shows that women aged 50-69 who are regularly screened are less likely to die from breast cancer." She cited an estimate from the International Agency for Research on Cancer (IARC) of the World Health Organisation which said mortality was reduced by 35% through screening — a figure Gøtzsche disputes in his book.

Gøtzsche's book tells of personal attacks on him and on other researchers by the pro-screening lobby, some of whom had financial interests in the continuation of screening programmes, he alleges.

He compares screening advocates to religious believers and argues that their hostile attitudes are harmful to scientific progress. A lot of false evidence has been put forward to claim that the screening effect was large, he writes. Those who tried to expose the errors came under personal attack, as if they were blasphemers.

"I cannot help wonder why many people shrug their shoulders when they learn of scientific misconduct and why many scientists don't care that they deceive their readers repeatedly and betray the confidence society has bestowed on them, whether for a political gain, for fame, for money, for getting research funding or for any other reason. People may keep on being dishonest, may get away with it and may publish in the same journals time and again, to the hurrahs of like-minded people who are often editors of the same journals," he writes.

Some of the screening trials were biased or badly done, the book says, for instance by deciding on the cause of death of a woman after researchers knew whether she had been screened for breast cancer or not. The best trials, it says, failed to prove that lives were saved by screening.

Gøtzsche's group also found that one in three cancers detected by screening was misdiagnosed.

Breast cancer deaths have gone down, he says, but better treatment and better-aware women, who go to the doctor as soon as they find a lump, are responsible. Half of all breast cancers are found between screenings, he says.

Gøtzsche and his group have been highly critical of the leaflet sent to women by the NHS screening programme, which, they say, inflates the benefits and discounts the harms. He says he is hopeful that something good will come of the review.

Klim McPherson, professor of public health epidemiology at Oxford University, has been a critic of the information given to women by the NHS and is also hopeful. He gives credit to Gøtzsche for his assiduous work over many years to get to the truth. "His Cochrane reviews of breast cancer screening are of extremely high quality and not to be lightly dismissed," he said.

Gøtzsche says his work is focused on helping women understand the risks and benefits of screening. In the book, he says one of the leaders of the Swedish trials claimed mammography was the best thing that had happened for women during the last 3,000 years and added: "There are still people who don't like mammography. Presumably they don't like women."

Gøtzsche sees it differently. "People who like women, and women themselves, should no longer accept the pervasive misinformation they have consistently been exposed to," he writes. "The collective denial and misrepresentation of facts about overdiagnosis and the little benefit there is of screening, if any, coupled with the disregard of the principles for informed consent and national laws, may be the biggest ethical scandal ever in healthcare.

"Hundreds of millions of women have been seduced into attending screening without knowing it could harm them. This violation of their human rights is the main reason we have done so much research on mammography screening and also why I have written this book."

http://www.guardian.co.uk/science/2012/jan/23/breast-cancer-screening-not-justified

APPLICATION OF SECOND GENERATION INFRARED IMAGING WITH COMPUTERIZED IMAGE ANALYSIS TO BREAST CANCER RISK ASSESSMENT

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ABSTRACT

Infrared imaging of the breast for breast cancer risk assessment with a second generation focal plane staring array system was found to produce images superior to a first generation scanning system. The second generation system had greater thermal sensitivity, more elements in the image and greater dynamic range, which resulted in a greater ability to demonstrate asymmetric heat patterns in the breasts of women being screened for breast cancer. The improved imaging of the second generation infrared system allowed more objective and quantitative visual analysis, compared to the very subjective qualitative results of the first generation infrared system. The greater sensitivity and resolution of the digitized images of the second generation infrared system also allowed image analysis of total breasts, breast quadrants and hot spots to produce mean, standard deviation, median, minimum and maximum temperatures.

KEY WORDS: Thermography, Infrared Imaging, Breast Cancer, Risk Assessment, Diagnosis

INTRODUCTION

Early studies of infrared (IR) imaging of the breast concentrated on its ability to diagnose breast cancer. Mammography and IR imaging, commonly called thermography in medicine, were compared for diagnostic ability during the Breast Cancer Detection and Demonstration Projects (USA) between 1973 and 1981, but IR imaging was discontinued after only a few years and no risk assessment or prognostic information was collected. Beginning in 1980 studies supporting the use of IR imaging in breast cancer risk assessment [1, 2, 3] and prognosis [3, 4] began to appear. The present study was designed to determine whether the improvements in IR technology that have been incorporated into the second generation focal plane indium antimonide detector IR imaging systems can improve the images used in breast cancer risk assessment.

METHODS

Patients at The Elliott Mastology Center (Baton Rouge, LA), who were being screened with mammography for breast cancer, underwent IR imaging of their breasts as part of their breast cancer risk assessment. During the study normal and high risk patients had IR images of their breasts taken with an Inframetrics scanning mercury cadmium telluride detector IR imaging system (right lateral, left lateral and frontal views) and recorded as hard copy photographic images (a color frontal isotherm view and three black and white views: frontal, left lateral and right lateral). For comparison 3 additional breast views (frontal, right lateral and left lateral) were recorded with an Amber focal plane indium antimonide staring array IR imaging system. IR images of 220 patients from both the scanning and focal plane systems were digitized and stored on computer hard disk, thus creating a digitized IR image database for later image analysis.

RESULTS

The focal plane array system produced much higher quality images than the scanning system. However the focal plane system often placed a great proportion of the patient's IR heat pattern beyond the upper limit of the heat range being recorded and thus blacked out the patient (black is hot in medical applications). The blacking out occurred because the averaging window for determining the temperature range had too much cool background when imaging thin patients. The first decision made was to try to quantitate the six individual asymmetric abnormalities that were present in the focal plane images and then to create an IR index by adding together the individual scores for each abnormality (small hot spot, score=1; large hot spot, score=2; global heat, score=3; vascular heat, score=1,2,3; areolar heat, score=1; edge heat, score=1). The focal plane images had IR indexes that ranged from 0 to 8 but the highest index computed was five. Previously, scanning IR images were abnormal if any of the six asymmetric abnormalities were present, and images that only had a borderline IR asymmetry were called slightly abnormal (3 levels of results: normal, slightly abnormal, abnormal).

The IR indexes derived from the second generation focal plane imaging results were compared to the levels of abnormality from the scanning results on the patients being screened for breast cancer. Chi-square analysis for independence showed that the two methods produced results that were strongly associated (p=.0001). The most interesting result was an increase in the sensitivity for asymmetric heat patterns with the focal plane system, as 50.5% (111 of 220) of the patients without breast cancer had

abnormal IR images, whereas only 32.7% (72 of 220) of the patients had asymmetric heat patterns with the scanning system. Analysis of the six asymmetric abnormalities individually showed that most of the increase in sensitivity could be attributed to a significant (p=.0038) increase in vascular asymmetry from 43 of 218 patients with the scanning system to 70 of 220 with the focal plane system. Next the distribution of the IR index was compared to the levels of abnormality from the scanning images to determine if the increase in sensitivity of the second generation technology would create small subsets with higher IR indexes that could be used to refine risk assessment. When an IR index of 1 is considered to be so insignificant that a patient's risk of getting breast cancer is not increased and 2 is considered to only slightly increase risk, then 14.1% (31 of 220) of the patients being screened for breast cancer would be categorized as high risk individuals. On the other hand 37 of 220 patients had abnormal IR images with the scanning system and this would mean that 16.8% of the screened patients would be at high risk.

Three known risk factors (family history of breast cancer, previous estrogen hormone therapy and previous breast biopsy) were compared to the IR results from the scanning and focal plane systems. None of these risk factors were found to correlate with the IR imaging results and therefore IR imaging results were found to be an independent risk factor in breast cancer. The physician also assigned patients being screened for breast cancer into normal and high risk categories by subjectively integrating family history, mastopathy, previous use of estrogen hormones and previous breast biopsy. The results of this physician integrated risk assessment was also not related to the IR imaging results.

The final part of the study was an attempt to apply image processing and computer vision techniques to produce objective measures of asymmetric heat patterns present in second generation IR images employed in breast cancer risk assessment. Preliminary results showed that comparative pixel statistics (mean, standard deviation, median, minimum, maximum temperatures) could be computed for complete breasts, quadrants of the breast and hot spots.

DISCUSSION

The improved image of the second generation IR imaging system was due to the greater thermal sensitivity, greater number of elements and greater dynamic range of the focal plane array imager. The one major drawback encountered in this study was blacking out of patients and this will be corrected in the future by adjusting the center of the temperature range (set at either 7.5 or 10°C) of the focal plane imager to optimally take in the temperature range of the patients. This procedure for temperature focusing has been routinely used with scanning IR imagers and has worked very well in breast cancer risk assessment.

The proportion of patients at increased risk of breast cancer

is probably still a little high with the second generation IR system, but the strength of the IR index is not in the overall proportion of patients that are at increased risk but with its ability to create different groups of patients at increased risk by adjusting the weight of the different abnormalities being inputted into the index. Future studies will be able to address the independent value of the 6 abnormalities and to create an index where the value of each abnormality will be appropriately weighted. This process of weighing the value of independent variables is not possible with the 3 level subjective analysis used with the scanning system.

In this study the lack of association between IR imaging results and known risk factors in patients being screened for breast cancer confirms that IR results are independent of known risk factors. Therefore, in light of the evidence [1, 2, 3] showing a strong association of asymmetric IR abnormalities of the breasts with a high risk of getting breast cancer, it can be concluded that abnormal IR images are a significant independent risk factor for breast cancer.

The comparative measurements resulting from the initial image analysis need to be done on a large database of focal plane images to determine their utility. Hopefully by removing the subjectivity of the present analysis and by providing additional information to the physician there will be an improvement in risk assessment by IR imaging. Models for the analysis of the breast IR images need to be developed that reduce perspective distortions that are inherent to imaging of 3 dimensional shapes and also to overcome the lack of ideal body symmetry due both to the natural asymmetry of the human body and also the spatial orientation of the imager to the subject. Finally the whole analysis must be automated, as highly interactive analysis is not conducive to the typical practice of medicine.

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Breast Cancer

What is cancer?

The body is made up of hundreds of millions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries.

Cancer begins when cells in a part of the body start to grow out of control. There are many kinds of cancer, but they all start because of out-of-control growth of abnormal cells.

Cancer cell growth is different from normal cell growth. Instead of dying, cancer cells continue to grow and form new, abnormal cells. Cancer cells can also invade (grow into) other tissues, something that normal cells cannot do. Growing out of control and invading other tissues are what makes a cell a cancer cell.

Cells become cancer cells because of damage to DNA. DNA is in every cell and directs all its actions. In a normal cell, when DNA gets damaged the cell either repairs the damage or the cell dies. In cancer cells, the damaged DNA is not repaired, but the cell doesn't die like it should. Instead, this cell goes on making new cells that the body does not need. These new cells will all have the same damaged DNA as the first cell does.

People can inherit damaged DNA, but most DNA damage is caused by mistakes that happen while the normal cell is reproducing or by something in our environment. Sometimes the cause of the DNA damage is something obvious, like cigarette smoking. But often no clear cause is found.

In most cases the cancer cells form a tumor. Some cancers, like leukemia, rarely form tumors. Instead, these cancer cells involve the blood and blood-forming organs and circulate through other tissues where they grow.

Cancer cells often travel to other parts of the body, where they begin to grow and form new tumors that replace normal tissue. This process is called metastasis. It happens when the cancer cells get into the bloodstream or lymph vessels of our body.

No matter where a cancer may spread, it is always named for the place where it started. For example, breast cancer that has spread to the liver is still called breast cancer, not liver cancer. Likewise, prostate cancer that has spread to the bone is metastatic prostate cancer, not bone cancer.

Different types of cancer can behave very differently. For example, lung cancer and breast cancer are very different diseases. They grow at different rates and respond to different treatments. That is why people with cancer need treatment that is aimed at their particular kind of cancer.

Not all tumors are cancerous. Tumors that aren't cancer are called benign. Benign tumors can cause problems – they can grow very large and press on healthy organs and tissues. But they cannot grow into (invade) other tissues. Because they can't invade, they also can't spread to other parts of the body (metastasize). These tumors are almost never life threatening.

What is breast cancer?

Breast cancer is a malignant tumor that starts from cells of the breast. A malignant tumor is a group of cancer cells that may grow into (invade) surrounding tissues or spread (metastasize) to distant areas of the body. The disease occurs almost entirely in women, but men can get it, too.

The remainder of this document refers only to breast cancer in women. For information on breast cancer in men, see our document, *Breast Cancer in Men***.**

The normal breast

To understand breast cancer, it helps to have some basic knowledge about the normal structure of the breasts, shown in the diagram below.

The female breast is made up mainly of *lobules* (milk-producing glands), *ducts* (tiny tubes that carry the milk from the lobules to the nipple), and *stroma* (fatty tissue and connective tissue surrounding the ducts and lobules, blood vessels, and lymphatic vessels).
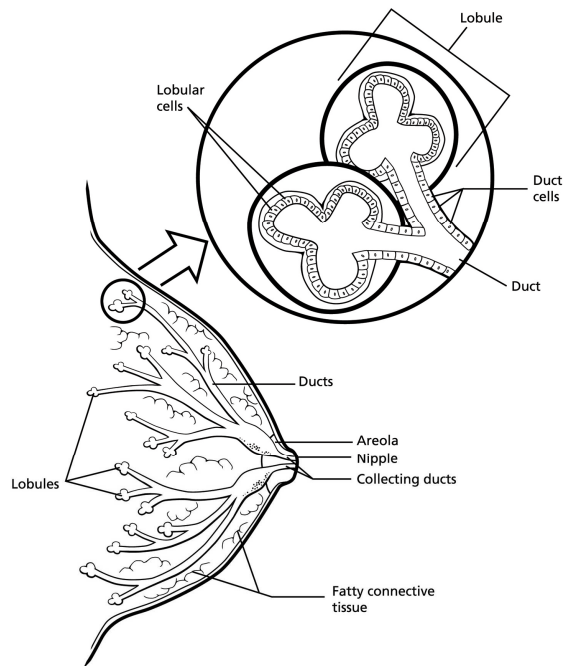
Most breast cancers begin in the cells that line the ducts (*ductal* cancers). Some begin in the cells that line the lobules (*lobular* cancers), while a small number start in other tissues.

The lymph (lymphatic) system

The lymph system is important to understand because it is one of the ways in which breast cancers can spread. This system has several parts.

Lymph nodes are small, bean-shaped collections of immune system cells (cells that are important in fighting infections) that are connected by lymphatic vessels. Lymphatic vessels are like small veins, except that they carry a clear fluid called lymph (instead of blood) away from the breast. Lymph contains tissue fluid and waste products, as well as immune system cells. Breast cancer cells can enter lymphatic vessels and begin to grow in lymph nodes.

Most lymphatic vessels in the breast connect to lymph nodes under the arm (*axillary nodes*). Some lymphatic vessels connect to lymph nodes inside the chest (*internal mammary nodes*) and those either above or below the collarbone (*supraclavicular* or *infraclavicular nodes*).

Supraclavicular lymph nodes

Infraclavicular lymph nodes

Axillary lymph nodes

Internal mammary lymph nodes

Axillary lymph nodes
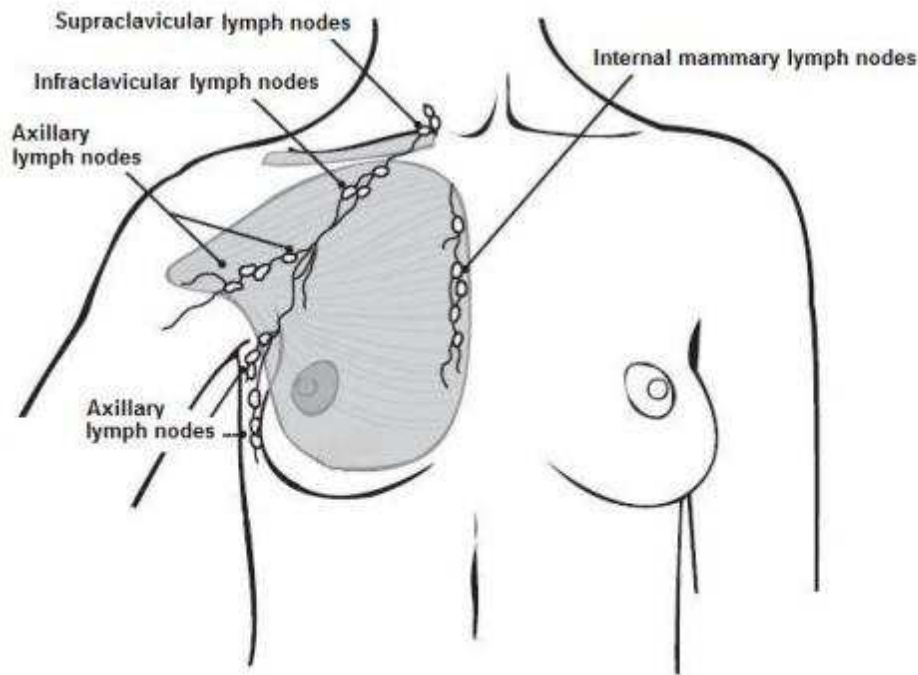
It is important to find out if the cancer cells have spread to lymph nodes because if they have, there is a higher chance that the cells could have also gotten into the bloodstream and spread (metastasized) to other sites in the body. The more lymph nodes that have breast cancer, the more likely it is that the cancer may be found in other organs as well. This is important to know because it could affect your treatment plan. Still, not all women with cancer cells in their lymph nodes develop metastases, and some women can have no cancer cells in their lymph nodes and later develop metastases.

Benign breast lumps

Most breast lumps are not cancerous (benign). Still, some may need to be sampled and viewed under a microscope to prove they are not cancer.

Fibrocystic changes

Most lumps turn out to be fibrocystic changes. The term *fibrocystic* refers to fibrosis and cysts. Fibrosis is the formation of scar-like (fibrous) tissue, and cysts are fluid-filled sacs. Fibrocystic changes can cause breast swelling and pain. This often happens just before a woman's menstrual period is about to begin. Her breasts may feel lumpy and, sometimes, she may notice a clear or slightly cloudy nipple discharge.

Other benign breast lumps

Benign breast tumors such as *fibroadenomas* or *intraductal papillomas* are abnormal growths, but they are not cancerous and do not spread outside of the breast to other organs. They are not life threatening. Still, some benign breast conditions are important because women with these conditions have a higher risk of developing breast cancer.

For more information see the section, "What are the risk factors for breast cancer?" and our document, *Non-cancerous Breast Conditions*.

General breast cancer terms

It is important to understand some of the key words used to describe breast cancer.

Carcinoma

This is a term used to describe a cancer that begins in the lining layer (epithelial cells) of organs like the breast. Nearly all breast cancers are carcinomas (either ductal carcinomas or lobular carcinomas).

Adenocarcinoma

An adenocarcinoma is a type of carcinoma that starts in glandular tissue (tissue that makes and secretes a substance). The ducts and lobules of the breast are glandular tissue (they make breast milk), so cancers starting in these areas are often called adenocarcinomas.

Carcinoma in situ

This term is used for the early stage of cancer, when it is confined to the layer of cells where it began. In breast cancer, *in situ* means that the cancer cells remain confined to ducts (ductal carcinoma in situ) or lobules (lobular carcinoma in situ). They have not grown into (*invaded*) deeper tissues in the breast or spread to other organs in the body. Carcinoma in situ of the breast is sometimes referred to as *non-invasive* or *pre-invasive* breast cancer.

Invasive (infiltrating) carcinoma

An invasive cancer is one that has already grown beyond the layer of cells where it started (as opposed to carcinoma in situ). Most breast cancers are invasive carcinomas -- either invasive ductal carcinoma or invasive lobular carcinoma.

Sarcoma

Sarcomas are cancers that start from connective tissues such as muscle tissue, fat tissue, or blood vessels. Sarcomas of the breast are rare.

Types of breast cancers

There are several types of breast cancer, but some of them are quite rare. In some cases a single breast tumor can have a combination of these types or have a mixture of invasive and in situ cancer.

Ductal carcinoma in situ

Ductal carcinoma in situ (DCIS; also known as *intraductal carcinoma*) is the most common type of non-invasive breast cancer. DCIS means that the cancer cells are inside the ducts but have not spread through the walls of the ducts into the surrounding breast tissue.

About 1 in 5 new breast cancer cases will be DCIS. Nearly all women diagnosed at this early stage of breast cancer can be cured. A mammogram is often the best way to find DCIS early.

When DCIS is diagnosed, the pathologist (a doctor specializing in diagnosing disease from tissue samples) will look for areas of dead or dying cancer cells, called *tumor necrosis*, within the tissue sample. If necrosis is present, the tumor is likely to be more aggressive. The term *comedocarcinoma* is often used to describe DCIS with necrosis.

Lobular carcinoma in situ

Although it is not a true cancer, lobular carcinoma in situ (LCIS; also called *lobular neoplasia*) is sometimes classified as a type of non-invasive breast cancer, which is why it is included here. It begins in the milk-producing glands but does not grow through the wall of the lobules.

Most breast cancer specialists think that LCIS itself does not become an invasive cancer very often, but women with this condition do have a higher risk of developing an invasive breast cancer in the same breast or in the opposite breast. For this reason, women with LCIS should make sure they have regular mammograms and doctor visits.

Invasive (or infiltrating) ductal carcinoma

This is the most common type of breast cancer. Invasive (or infiltrating) ductal carcinoma (IDC) starts in a milk passage (duct) of the breast, breaks through the wall of the duct, and grows into the fatty tissue of the breast. At this point, it may be able to spread (metastasize) to other parts of the body through the lymphatic system and bloodstream. About 8 of 10 invasive breast cancers are infiltrating ductal carcinomas.

Invasive (or infiltrating) lobular carcinoma

Invasive lobular carcinoma (ILC) starts in the milk-producing glands (lobules). Like IDC, it can spread (metastasize) to other parts of the body. About 1 out of 10 invasive breast cancers is an ILC. Invasive lobular carcinoma may be harder to detect by a mammogram than invasive ductal carcinoma.

Less common types of breast cancer

Inflammatory breast cancer: This uncommon type of invasive breast cancer accounts for about 1% to 3% of all breast cancers. Usually there is no single lump or tumor. Instead, inflammatory breast cancer (IBC) makes the skin of the breast look red and feel warm. It also gives the breast skin a thick, pitted appearance that looks a lot like an orange peel. Doctors now know that these changes are not caused by inflammation or infection, but by cancer cells blocking lymph vessels in the skin. The affected breast may become larger or firmer, tender, or itchy. In its early stages, inflammatory breast cancer is often mistaken for an infection in the breast (called *mastitis*). Often this cancer is first treated as an infection with antibiotics. If the symptoms are caused by cancer, they will not improve, and the skin may be biopsied to look for cancer cells. Because there is no actual lump, it may not show up on a mammogram, which may make it even harder to find it early. This type of breast cancer tends to have a higher chance of spreading and a worse outlook than typical invasive ductal or lobular cancer. For more details about this condition, see our document, *Inflammatory Breast Cancer.*

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Triple-negative breast cancer: This term is used to describe breast cancers (usually invasive ductal carcinomas) whose cells lack estrogen receptors and progesterone receptors, and do not have an excess of the HER2 protein on their surfaces. (See the section, "How is breast cancer diagnosed?" for more detail on these receptors.) Breast cancers with these characteristics tend to occur more often in younger women and in African-American women. Triple-negative breast cancers tend to grow and spread more quickly than most other types of breast cancer. Because the tumor cells lack these certain receptors, neither hormone therapy nor drugs that target HER2 are effective against these cancers (but chemotherapy can still be useful if needed).

Mixed tumors: Mixed tumors contain a variety of cell types, such as invasive ductal cancer combined with invasive lobular breast cancer. In this situation, the tumor is treated as if it were an invasive ductal cancer.

Medullary carcinoma: This special type of infiltrating breast cancer has a rather well-defined boundary between tumor tissue and normal tissue. It also has some other special features, including the large size of the cancer cells and the presence of immune system cells at the edges of the tumor. Medullary carcinoma accounts for about 3% to 5% of breast cancers. The outlook (prognosis) for this kind of breast cancer is generally better than for the more common types of invasive breast cancer. Most cancer specialists think that true medullary cancer is very rare, and that cancers that are called medullary cancer should be treated as the usual invasive ductal breast cancer.

Metaplastic carcinoma: Metaplastic carcinoma (also known as carcinoma with metaplasia) is a very rare type of invasive ductal cancer. These tumors include cells that are normally not found in the breast, such as cells that look like skin cells (squamous cells) or cells that make bone. These tumors are treated like invasive ductal cancer.

Mucinous carcinoma: Also known as colloid carcinoma, this rare type of invasive breast cancer is formed by mucus-producing cancer cells. The prognosis for mucinous

carcinoma is usually better than for the more common types of invasive breast cancer. Still, it is treated like invasive ductal carcinoma.

Paget disease of the nipple: This type of breast cancer starts in the breast ducts and spreads to the skin of the nipple and then to the areola, the dark circle around the nipple. It is rare, accounting for only about 1% of all cases of breast cancer. The skin of the nipple and areola often appears crusted, scaly, and red, with areas of bleeding or oozing. The woman may notice burning or itching.

Paget disease is almost always associated with either ductal carcinoma in situ (DCIS) or, more often, with infiltrating ductal carcinoma. Treatment often requires mastectomy. If only DCIS is found (with no invasive cancer) when the breast is removed, the outlook is excellent.

Tubular carcinoma: Tubular carcinomas are another special type of invasive ductal breast carcinoma. They are called tubular because of the way the cells are arranged when seen under the microscope. Tubular carcinomas account for about 2% of all breast cancers. They are treated like invasive ductal carcinomas, but tend to have a better prognosis than most breast cancers.

Papillary carcinoma: The cells of these cancers tend to be arranged in small, finger-like projections when viewed under the microscope. These tumors can be separated into non-invasive and invasive types. Intraductal papillary carcinoma or papillary carcinoma in situ is non-invasive. It is often considered a subtype of ductal carcinoma in situ (DCIS), and is treated as such. In rare cases, the tumor is invasive, in which case it is treated like invasive ductal carcinoma, although the outlook is likely to be better. These cancers tend to be diagnosed in older women, and they make up no more than 1% or 2% of all breast cancers.

Adenoid cystic carcinoma (adenocystic carcinoma): These cancers have both glandular (adenoid) and cylinder-like (cystic) features when seen under the microscope. They make up less than 1% of breast cancers. They rarely spread to the lymph nodes or distant areas, and they tend to have a very good prognosis.

Phyllodes tumor: This very rare breast tumor develops in the stroma (connective tissue) of the breast, in contrast to carcinomas, which develop in the ducts or lobules. Other names for these tumors include *phylloides tumor* and *cystosarcoma phyllodes*. These tumors are usually benign but on rare occasions may be malignant.

Benign phyllodes tumors are treated by removing the tumor along with a margin of normal breast tissue. A malignant phyllodes tumor is treated by removing it along with a wider margin of normal tissue, or by mastectomy. Surgery is often all that is needed, but these cancers may not respond as well to the other treatments used for more common breast cancers. When a malignant phyllodes tumor has spread, it may be treated with the chemotherapy given for soft-tissue sarcomas (this is discussed in detail in our document, *Soft-tissue Sarcomas*.

Angiosarcoma: This is a form of cancer that starts from cells that line blood vessels or lymph vessels. It rarely occurs in the breasts. When it does, it usually develops as a

complication of previous radiation treatments. This is an extremely rare complication of breast radiation therapy that can develop about 5 to 10 years after radiation. Angiosarcoma can also occur in the arm of women who develop lymphedema as a result of lymph node surgery or radiation therapy to treat breast cancer. (For information on lymphedema, see the section, "How is breast cancer treated?") These cancers tend to grow and spread quickly. Treatment is generally the same as for other sarcomas. See our document, *Sarcoma - Adult Soft Tissue Cancer.*

What are the key statistics about breast cancer?

Breast cancer is the most common cancer among American women, except for skin cancers. The chance of developing invasive breast cancer at some time in a woman's life is a little less than 1 in 8 (12%).

The American Cancer Society's most recent estimates for breast cancer in the United States are for 2010:

- About 207,090 new cases of invasive breast cancer will be diagnosed in women.

- About 54,010 new cases of carcinoma in situ (CIS) will be diagnosed (CIS is non-invasive and is the earliest form of breast cancer).

- About 39,840 women will die from breast cancer

After increasing for more than 2 decades, female breast cancer incidence rates decreased by about 2% per year from 1998 to 2007. This decrease was seen only in women aged 50 or older, and may be due at least in part to the decline in use of hormone therapy after menopause that occurred after the results of the Women's Health Initiative were published in 2002. This study linked the use of hormone therapy to an increased risk of breast cancer and heart diseases.

Breast cancer is the second leading cause of cancer death in women, exceeded only by lung cancer. The chance that breast cancer will be responsible for a woman's death is about 1 in 35 (about 3%). Death rates from breast cancer have been declining since about 1990, with larger decreases in women younger than 50. These decreases are believed to be the result of earlier detection through screening and increased awareness, as well as improved treatment.

At this time there are over 2.5 million breast cancer survivors in the United States. (This includes women still being treated and those who have completed treatment.) Survival rates are discussed in the section "How is breast cancer staged?"

What are the risk factors for breast cancer?

A risk factor is anything that affects your chance of getting a disease, such as cancer. Different cancers have different risk factors. For example, exposing skin to strong sunlight is a risk factor for skin cancer. Smoking is a risk factor for cancers of the lung, mouth, larynx (voice box), bladder, kidney, and several other organs.

But risk factors don't tell us everything. Having a risk factor, or even several, does not mean that you will get the disease. Most women who have one or more breast cancer risk factors never develop the disease, while many women with breast cancer have no apparent risk factors (other than being a woman and growing older). Even when a woman with risk factors develops breast cancer, it is hard to know just how much these factors may have contributed to her cancer.

There are different kinds of risk factors. Some factors, like a person's age or race, can't be changed. Others are linked to cancer-causing factors in the environment. Still others are related personal behaviors, such as smoking, drinking, and diet. Some factors influence risk more than others, and your risk for breast cancer can change over time, due to factors such as aging or lifestyle.

Risk factors you cannot change

Gender

Simply being a woman is the main risk factor for developing breast cancer. Although women have many more breast cells than men, the main reason they develop more breast cancer is because their breast cells are constantly exposed to the growth-promoting effects of the female hormones estrogen and progesterone. Men can develop breast cancer, but this disease is about 100 times more common among women than men.

Aging

Your risk of developing breast cancer increases as you get older. About 1 out of 8 invasive breast cancers are found in women younger than 45, while about 2 out of 3 invasive breast cancers are found in women age 55 or older.

Genetic risk factors

About 5% to 10% of breast cancer cases are thought to be hereditary, resulting directly from gene defects (called *mutations*) inherited from a parent. See the section, "Do we know what causes breast cancer?" for more information about genes and DNA.

BRCA1 and BRCA2: The most common cause of hereditary breast cancer is an inherited mutation in the BRCA1 and BRCA2 genes. In normal cells, these genes help prevent cancer by making proteins that help keep the cells from growing abnormally. If you have inherited a mutated copy of either gene from a parent, you have a high risk of

developing breast cancer during your lifetime. The risk may be as high as 80% for members of some families with BRCA mutations. These cancers tend to occur in younger women and more often affect both breasts than cancers in women who are not born with one of these gene mutations. Women with these inherited mutations also have an increased risk for developing other cancers, particularly ovarian cancer.

In the UnitedStates BRCA mutations are found most often in Jewish women of Ashkenazi (Eastern Europe) origin, but they can occur in any racial or ethnic group.

Changes in other genes: Other gene mutations can also lead to inherited breast cancers. These gene mutations are much rarer and often do not increase the risk of breast cancer as much as the BRCA genes. They are not frequent causes of inherited breast cancer.

- ATM: The ATM gene normally helps repair damaged DNA. Inheriting 2 abnormal copies of this gene causes the disease ataxia-telangiectasia. Inheriting one mutated copy of this gene has been linked to a high rate of breast cancer in some families.

- p53: Inherited mutations of the p53 tumor suppressor gene cause the Li-Fraumeni syndrome (named after the 2 researchers who first described it). People with this syndrome have an increased the risk of developing breast cancer, as well as several other cancers such as leukemia, brain tumors, and sarcomas (cancer of bones or connective tissue). This is a rare cause of breast cancer.

- CHEK2: The Li-Fraumeni syndrome can also be caused by inherited mutations in the CHEK2 gene. Even when it does not cause this syndrome, it can increase breast cancer risk about twofold when it is mutated.

- PTEN: The PTEN gene normally helps regulate cell growth. Inherited mutations in this gene cause Cowden syndrome, a rare disorder in which people are at increased risk for both benign and malignant breast tumors, as well as growths in the digestive tract, thyroid, uterus, and ovaries.

- CDH1: Inherited mutations in this gene cause hereditary diffuse gastric cancer, a syndrome in which people develop a rare type of stomach cancer at an early age. Women with mutations in this gene also have an increased risk of invasive lobular breast cancer.

Genetic testing: Genetic tests can be done to look for mutations in the BRCA1 and BRCA2 genes (or less commonly in other genes such as PTEN or p53). Although testing may be helpful in some situations, the pros and cons need to be considered carefully. For more information, see the section, "Can breast cancer be prevented?"

Family history of breast cancer

Breast cancer risk is higher among women whose close blood relatives have this disease.

Having one first-degree relative (mother, sister, or daughter) with breast cancer approximately doubles a woman's risk. Having 2 first-degree relatives increases her risk about 3-fold.

The exact risk is not known, but women with a family history of breast cancer in a father or brother also have an increased risk of breast cancer. Altogether, less than 15% of women with breast cancer have a family member with this disease. This means that most (over 85%) women who get breast cancer *do not* have a family history of this disease.

Personal history of breast cancer

A woman with cancer in one breast has a 3- to 4-fold increased risk of developing a new cancer in the other breast or in another part of the same breast. This is different from a recurrence (return) of the first cancer.

Race and ethnicity

White women are slightly more likely to develop breast cancer than are African-American women. African-American women are more likely to die of this cancer. At least part of this seems to be because African-American women tend to have more aggressive tumors, although why this is the case is not known. Asian, Hispanic, and Native-American women have a lower risk of developing and dying from breast cancer.

Dense breast tissue

Women with denser breast tissue (as seen on a mammogram) have more glandular tissue and less fatty tissue, and have a higher risk of breast cancer. Unfortunately, dense breast tissue can also make it harder for doctors to spot problems on mammograms.

Certain benign breast conditions

Women diagnosed with certain benign breast conditions may have an increased risk of breast cancer. Some of these conditions are more closely linked to breast cancer risk than others. Doctors often divide benign breast conditions into 3 general groups, depending on how they affect this risk.

Non-proliferative lesions: These conditions are not associated with overgrowth of breast tissue. They do not seem to affect breast cancer risk, or if they do, it is to a very small extent. They include:

- Fibrocystic disease (fibrosis and/or cysts)
- Mild hyperplasia
- Adenosis (non-sclerosing)
- Duct ectasia
- Phyllodes tumor (benign)
- A single papilloma
- Fat necrosis

- Mastitis (infection of the breast)

- Simple fibroadenoma

- Other benign tumors (lipoma, hamartoma, hemangioma, neurofibroma)

Proliferative lesions without atypia: These conditions show excessive growth of cells in the ducts or lobules of the breast tissue. They seem to raise a woman's risk of breast cancer slightly (1½ to 2 times normal). They include:

- Usual ductal hyperplasia (without atypia)

- Complex fibroadenoma

- Sclerosing adenosis

- Several papillomas (called papillomatosis)

- Radial scar

Proliferative lesions with atypia: In these conditions, there is excessive growth of cells in the ducts or lobules of the breast tissue, and the cells no longer appear normal. They have a stronger effect on breast cancer risk, raising it 4 to 5 times higher than normal. They include:

- Atypical ductal hyperplasia (ADH)

- Atypical lobular hyperplasia (ALH)

Women with a family history of breast cancer and either hyperplasia or atypical hyperplasia have an even higher risk of developing a breast cancer.

For more information on these conditions, see our document, *Non-cancerous Breast Conditions*.

Lobular carcinoma in situ

Women with lobular carcinoma in situ (LCIS) have a 7- to 11-fold increased risk of developing cancer in either breast.

Menstrual periods

Women who have had more menstrual cycles because they started menstruating at an early age (before age 12) and/or went through menopause at a later age (after age 55) have a slightly higher risk of breast cancer. This may be related to a higher lifetime exposure to the hormones estrogen and progesterone.

Previous chest radiation

Women who, as children or young adults, had radiation therapy to the chest area as treatment for another cancer (such as Hodgkin disease or non-Hodgkin lymphoma) are at significantly increased risk for breast cancer. This varies with the patient's age when they

had radiation. If chemotherapy was also given, it may have stopped ovarian hormone production for some time, lowering the risk. The risk of developing breast cancer from chest radiation is highest if the radiation was given during adolescence, when the breasts were still developing. Radiation treatment after age 40 does not seem to increase breast cancer risk.

Diethylstilbestrol exposure

From the 1940s through the 1960s some pregnant women were given the drug diethylstilbestrol (DES) because it was thought to lower their chances of miscarriage (losing the baby). These women have a slightly increased risk of developing breast cancer. Women whose mothers took DES during pregnancy may also have a slightly higher risk of breast cancer. For more information on DES see our document, *DES Exposure: Questions and Answers*.

Lifestyle-related factors and breast cancer risk

Having children

Women who have had no children or who had their first child after age 30 have a slightly higher breast cancer risk. Having many pregnancies and becoming pregnant at a young age reduce breast cancer risk. Pregnancy reduces a woman's total number of lifetime menstrual cycles, which may be the reason for this effect.

Recent oral contraceptive use

Studies have found that women using oral contraceptives (birth control pills) have a slightly greater risk of breast cancer than women who have never used them. This risk seems to decline back to normal over time once the pills are stopped. Women who stopped using oral contraceptives more than 10 years ago do not appear to have any increased breast cancer risk. When thinking about using oral contraceptives, women should discuss their other risk factors for breast cancer with their health care team.

Hormone therapy after menopause

Hormone therapy with estrogen (sometimes with progesterone) has been used for many years to help relieve symptoms of menopause and to help prevent osteoporosis (thinning of the bones). Earlier studies suggested it might have other health benefits as well, but these benefits have not been found in more recent, better designed studies. This treatment goes by many names, such as *post-menopausal hormone therapy* (PHT), *hormone replacement therapy* (HRT), and *menopausal hormone therapy* (MHT).

There are 2 main types of hormone therapy. For women who still have a uterus (womb), doctors generally prescribe both estrogen and progesterone (known as *combined hormone therapy* or *HT*). Because estrogen alone can increase the risk of cancer of the uterus, progesterone is added to help prevent this. For women who no longer have a uterus (those

who've had a hysterectomy), estrogen alone can be prescribed. This is commonly known as *estrogen replacement therapy* (ERT) or just *estrogen therapy (ET)*.

Combined hormone therapy: Using combined hormone therapy after menopause increases the risk of getting breast cancer. It may also increase the chances of dying from breast cancer. This increase in risk can be seen with as little as 2 years of use. Combined HT also increases the likelihood that the cancer may be found at a more advanced stage, possibly because it reduces the effectiveness of mammograms by increasing breast density.

The increased risk from combined hormone therapy appears to apply only to current and recent users. A woman's breast cancer risk seems to return to that of the general population within 5 years of stopping combined treatment.

ERT: The use of estrogen alone after menopause does not appear to increase the risk of developing breast cancer significantly, if at all. But when used long term (for more than 10 years), ERT has been found to increase the risk of ovarian and breast cancer in some studies.

At this time there appear to be few strong reasons to use post-menopausal hormone therapy (either combined HT or ET), other than possibly for the short-term relief of menopausal symptoms. Along with the increased risk of breast cancer, combined HT also appears to increase the risk of heart disease, blood clots, and strokes. It does lower the risk of colorectal cancer and osteoporosis, but this must be weighed against possible harm, especially since there are other effective ways to prevent and treat osteoporosis. Although ET does not seem to have much effect on breast cancer risk, it does increase the risk of stroke. The increased risk of hormone therapy is the same for "bioidentical" and "natural" hormones as it is for synthetic hormones.

The decision to use hormone therapy after menopause should be made by a woman and her doctor after weighing the possible risks and benefits, based on the severity of her menopausal symptoms and the woman's other risk factors for heart disease, breast cancer, and osteoporosis. If a woman and her doctor decide to try hormones for symptoms of menopause, it is usually best to use it at the lowest dose needed to control symptoms and for as short a time as possible.

Breast-feeding

Some studies suggest that breast-feeding may slightly lower breast cancer risk, especially if breast-feeding is continued for 1½ to 2 years. But this has been a difficult area to study, especially in countries such as the United States, where breast-feeding for this long is uncommon.

The explanation for this possible effect may be that breast-feeding reduces a woman's total number of lifetime menstrual cycles (similar to starting menstrual periods at a later age or going through early menopause).

Alcohol

The use of alcohol is clearly linked to an increased risk of developing breast cancer. The risk increases with the amount of alcohol consumed. Compared with non-drinkers, women who consume 1 alcoholic drink a day have a very small increase in risk. Those who have 2 to 5 drinks daily have about 1½ times the risk of women who drink no alcohol. Excessive alcohol use is also known to increase the risk of developing cancers of the mouth, throat, esophagus, and liver. The American Cancer Society recommends that women limit their consumption of alcohol to no more than one drink a day.

Being overweight or obese

Being overweight or obese has been found to increase breast cancer risk, especially for women after menopause. Before menopause your ovaries produce most of your estrogen, and fat tissue produces a small amount of estrogen. After menopause (when the ovaries stop making estrogen), most of a woman's estrogen comes from fat tissue. Having more fat tissue after menopause can increase your chance of getting breast cancer by raising estrogen levels. Also, women who are overweight tend to have higher blood insulin levels. Higher insulin levels have also been linked to some cancers, including breast cancer.

But the connection between weight and breast cancer risk is complex. For example, the risk appears to be increased for women who gained weight as an adult but may not be increased among those who have been overweight since childhood. Also, excess fat in the waist area may affect risk more than the same amount of fat in the hips and thighs. Researchers believe that fat cells in various parts of the body have subtle differences that may explain this.

The American Cancer Society recommends you maintain a healthy weight throughout your life by balancing your food intake with physical activity and avoiding excessive weight gain.

Physical activity

Evidence is growing that physical activity in the form of exercise reduces breast cancer risk. The main question is how much exercise is needed. In one study from the Women's Health Initiative (WHI) as little as 1.25 to 2.5 hours per week of brisk walking reduced a woman's risk by 18%. Walking 10 hours a week reduced the risk a little more.

To reduce your risk of breast cancer, the American Cancer Society recommends 45 to 60 minutes of intentional physical activity 5 or more days a week.

Factors with uncertain, controversial, or unproven effect on breast cancer risk

Diet and vitamin intake

Many studies have looked for a link between certain diet and breast cancer risk, but so far the results have been conflicting. Some studies have indicated that diet may play a role, while others found no evidence that diet influences breast cancer risk. Studies have looked at the amount of fat in the diet, intake of fruits and vegeatables, and intake of meat. No clear link to breast cancer risk was found. Studies have also looked at vitamin levels, again with inconsistent results. Some studies actually found an increased risk of breast cancer in women with higher levels of certain nutrients. Also, so far, no study has shown that taking vitamins reduces breast cancer risk. This is not to say that there is no point in eating a healthy diet. A diet low in fat, low in red meat and processed meat, and high in fruits and vegeatables may have other health benefits.

Most studies have found that breast cancer is less common in countries where the typical diet is low in total fat, low in polyunsaturated fat, and low in saturated fat. On the other hand, many studies of women in the United States have not found breast cancer risk to be related to dietary fat intake. Researchers are still not sure how to explain this apparent disagreement. It may be at least partly due to the effect of diet on body weight (see below). Also, studies comparing diet and breast cancer risk in different countries are complicated by other differences (like activity level, intake of other nutrients, and genetic factors) that might also change breast cancer risk.

More research is needed to better understand the effect of the types of fat eaten on breast cancer risk. But it is clear that calories do count, and fat is a major source of these. High-fat diets can lead to being overweight or obese, which is a breast cancer risk factor. A diet high in fat has also been shown to influence the risk of developing several other types of cancer, and intake of certain types of fat is clearly related to heart disease risk.

The American Cancer Society recommends eating a healthy diet with an emphasis on plant sources. This includes eating 5 or more servings of vegetables and fruits each day, choosing whole grains over those that are processed (refined), and limiting consumption of processed and red meats.

Antiperspirants

Internet e-mail rumors have suggested that chemicals in underarm antiperspirants are absorbed through the skin, interfere with lymph circulation, cause toxins to build up in the breast, and eventually lead to breast cancer. There is very little laboratory or population-based evidence to support this rumor.

One small study has found trace levels of parabens (used as preservatives in antiperspirants and other products), which have weak estrogen-like properties, in a small sample of breast cancer tumors. But this study did not look at whether parabens caused the tumors. This was a preliminary finding, and more research is needed to determine

what effect, if any, parabens may have on breast cancer risk. On the other hand, a large study of breast cancer causes found no increase in breast cancer in women who used underarm antiperspirants and/or shaved their underarms.

Bras

Internet e-mail rumors and at least one book have suggested that bras cause breast cancer by obstructing lymph flow. There is no good scientific or clinical basis for this claim. Women who do not wear bras regularly are more likely to be thinner or have less dense breasts, which would probably contribute to any perceived difference in risk.

Induced abortion

Several studies have provided very strong data that neither induced abortions nor spontaneous abortions (miscarriages) have an overall effect on the risk of breast cancer. For more detailed information, see our document, *Is Abortion Linked to Breast Cancer?*

Breast implants

Several studies have found that breast implants do not increase breast cancer risk, although silicone breast implants can cause scar tissue to form in the breast. Implants make it harder to see breast tissue on standard mammograms, but additional x-ray pictures called implant displacement views can be used to examine the breast tissue more completely.

Chemicals in the environment

A great deal of research has been reported and more is being done to understand possible environmental influences on breast cancer risk.

Of special interest are compounds in the environment that have been found in lab studies to have estrogen-like properties, which could in theory affect breast cancer risk. For example, substances found in some plastics, certain cosmetics and personal care products, pesticides (such as DDE), and PCBs (polychlorinated biphenyls) seem to have such properties.

This issue understandably invokes a great deal of public concern, but at this time research does not show a clear link between breast cancer risk and exposure to these substances. Unfortunately, studying such effects in humans is difficult. More research is needed to better define the possible health effects of these and similar substances.

Tobacco smoke

Most studies have found no link between cigarette smoking and breast cancer. Some studies have suggested smoking increases the risk of breast cancer, but this remains controversial.

An active focus of research is whether secondhand smoke increases the risk of breast cancer. Both mainstream and secondhand smoke contain chemicals that, in high concentrations, cause breast cancer in rodents. Chemicals in tobacco smoke reach breast tissue and are found in breast milk.

The evidence on secondhand smoke and breast cancer risk in human studies is controversial, at least in part because smokers have not been shown to be at increased risk. One possible explanation for this is that tobacco smoke may have different effects on breast cancer risk in smokers and in those who are just exposed to smoke.

A report from the California Environmental Protection Agency in 2005 concluded that the evidence about secondhand smoke and breast cancer is "consistent with a causal association" in younger, mainly premenopausal women. The 2006 US Surgeon General's report, *The Health Consequences of Involuntary Exposure to Tobacco Smoke*, concluded that there is "suggestive but not sufficient" evidence of a link at this point. In any case, this possible link to breast cancer is yet another reason to avoid secondhand smoke.

Night work

Several studies have suggested that women who work at night -- for example, nurses on a night shift -- may have an increased risk of developing breast cancer. This is a fairly recent finding, and more studies are looking at this issue. Some researchers think the effect may be due to changes in levels of melatonin, a hormone whose production is affected by the body's exposure to light, but other hormones are also being studied.

Do we know what causes breast cancer?

Many risk factors may increase your chance of developing breast cancer, but it is not yet known exactly how some of these risk factors cause cells to become cancerous. Hormones seem to play a role in many cases of breast cancer, but just how this happens is not fully understood.

Certain changes in DNA can cause normal breast cells to become cancerous. DNA is the chemical in each of our cells that makes up our genes -- the instructions for how our cells function. We usually look like our parents because they are the source of our DNA. But DNA affects more than how we look.

Some genes contain instructions for controlling when our cells grow, divide, and die. Certain genes that speed up cell division are called *oncogene*s. Others that slow down cell division, or cause cells to die at the right time, are called *tumor suppressor genes*. Cancers can be caused by DNA mutations (changes) that "turn on" oncogenes or "turn off" tumor suppressor genes.

Inherited gene mutations

Certain inherited DNA changes can increase the risk for developing cancer and are responsible for the cancers that run in some families. For example, the BRCA genes

(BRCA1 and BRCA2) are tumor suppressor genes. Mutations in these genes can be inherited from parents. When they are mutated, they no longer suppress abnormal growth, and cancer is more likely to develop.

Women have already begun to benefit from advances in understanding the genetic basis of breast cancer. Genetic testing can identify some women who have inherited mutations in the BRCA1 or BRCA2 tumor suppressor genes (or less commonly in other genes such as PTEN or p53). These women can then take steps to reduce their risk of developing breast cancers and to monitor changes in their breasts carefully to find cancer at an earlier, more treatable stage. These are discussed in the following sections of this document.

Acquired gene mutations

Most DNA mutations related to breast cancer occur in single breast cells during a woman's life rather than having been inherited. These *acquired* mutations of oncogenes and/or tumor suppressor genes may result from other factors, like radiation or cancer-causing chemicals. But so far, the causes of most acquired mutations that could lead to breast cancer remain unknown. Most breast cancers have several gene mutations that are acquired.

Tests to spot acquired gene changes may help doctors more accurately predict the outlook for some women with breast cancer. For example, tests can identify women whose breast cancer cells have too many copies of the HER2 oncogene. These cancers tend to be more aggressive. At the same time, drugs have been developed that specifically target these cancers.

Can breast cancer be prevented?

There is no sure way to prevent breast cancer. But there are things all women can do that might reduce their risk and help increase the odds that if cancer does occur, it is found at an early, more treatable stage.

Lowering your risk

You can lower your risk of breast cancer by changing those risk factors that can be changed (see the section, "What are the risk factors for breast cancer?"). Women who limit alcohol intake, exercise regularly, and maintain a healthy body weight have a lower risk of getting breast cancer. Women who choose to breast-feed for at least several months may also get an added benefit of reducing their breast cancer risk.

Not using hormone therapy after menopause can help you avoid raising your risk.

It's not clear at this time if environmental chemicals that have estrogen-like properties (like those found in some plastic bottles or certain cosmetics and personal care products) increase breast cancer risk. If there is an increased risk, it is likely to be very small. Still,

women who are concerned may choose to avoid products that contain these substances when possible.

Finding breast cancer early

Other than lifestyle changes, the most important action a woman can take is to follow early detection guidelines. Following the American Cancer Society's guidelines for early detection (outlined in the section, "Can breast cancer be found early?") will not prevent breast cancer, but it can help find cancers when the likelihood of successful treatment is greatest.

For women who are or may be at increased risk

If you are a woman at increased risk for breast cancer (for example, because you have a strong family history of breast cancer, a known genetic mutation of a BRCA gene, or you have had DCIS, LCIS, or biopsies that have shown pre-cancerous changes), there may be some things you can do to reduce your chances of developing breast cancer. Before deciding which, if any, of these may be right for you, talk with your doctor to understand what your risk is and how much any of these approaches might lower this risk.

Genetic testing for BRCA gene mutations

Many women may have relatives with breast cancer, but in most cases this is not the result of BRCA gene mutations. Genetic testing for these mutations can expensive and the results are often not clear cut. Testing can have a wide range of consequences that need to be considered. It should only be done when there is a reasonable suspicion that a mutation may be present.

The U.S. Preventive Services Task Force (USPSTF) recommends that only women with a strong family history be evaluated for genetic testing for BRCA mutations. This group represents only about 2% of adult women in the United States.

The USPSTF recommends that women who are not of Ashkenazi (Eastern European) Jewish heritage should be referred for genetic evaluation if they have any of the following:

- 2 first-degree relatives (mother, sisters, daughters) with breast cancer, one of whom was diagnosed when they were younger than 50

- 3 or more first- or second-degree relatives (includes grandmothers, aunts) diagnosed with breast cancer

- Both breast and ovarian cancer among first- and second-degree relatives

- A first-degree relative diagnosed with cancer in both breasts

- 2 or more first- or second-degree relatives diagnosed with ovarian cancer

- A male relative with breast cancer

Women of Ashkenazi (Eastern European) Jewish heritage should be referred for genetic evaluation if they have:

- A first-degree relative with breast or ovarian cancer

- 2 second-degree relatives on the same side of the family with breast or ovarian cancer

If you are considering genetic testing, it is strongly recommended that you talk first to a genetic counselor, nurse, or doctor qualified to explain and interpret the results of these tests. It is very important to understand what genetic testing can and can't tell you, and to carefully weigh the benefits and risks of testing before these tests are done. Testing is expensive and may not be covered by some health insurance plans.

For more information, see our document, *Genetic Testing: What You Need to Know*. You may also want to visit the National Cancer Institute web site (www.cancer.gov/cancertopics/Genetic-Testing-for-Breast-and-Ovarian-Cancer-Risk).

Breast cancer chemoprevention

Chemoprevention is the use of drugs to reduce the risk of cancer. Several drugs have been studied for use in lowering breast cancer risk.

Tamoxifen: Tamoxifen is a drug that blocks some of the effects of estrogen on breast tissue. It has been used for many years to reduce the risk of recurrence in localized breast cancer and as a treatment for advanced breast cancer when the tumor is estrogen-receptor positive (see the section, "How is breast cancer treated?"). Several studies have found that tamoxifen can also lower the risk of getting breast cancer in women who are at increased risk for the disease.

Results from the Breast Cancer Prevention Trial (BCPT) have shown that women at increased risk for breast cancer are less likely to develop the disease if they take tamoxifen. Women in the study took either tamoxifen or a placebo pill for 5 years. After 7 years of follow-up, women taking tamoxifen had 42% fewer breast cancers than women who took the placebo, although there was no difference in the risk of dying from breast cancer. Tamoxifen is approved for reducing breast cancer risk in women at high risk.

Tamoxifen has side effects that include increased risks of endometrial (uterine) cancer and blood clotting, so women should consider the possible benefits and risks of tamoxifen before deciding if it is right for them.

And while amoxifen seems to reduce breast cancer risk in women with BRCA2 gene mutations, the same may not be true for those with BRCA1 mutations.

Raloxifene: Like tamoxifen, raloxifene also blocks the effect of estrogen on breast tissue. A study comparing the effectiveness of the 2 drugs in women after menopause, called the Study of Tamoxifen and Raloxifene (STAR) trial, found that raloxifene worked nearly as well as tamoxifen in reducing the risk of invasive breast cancer and non-invasive cancer (DCIS or LCIS). Raloxifene also had lower risks of certain side effects such as uterine cancer and blood clots in the legs or lungs, compared to tamoxifen (although the risk of blood clots was still higher than normal).

Raloxifene is approved to help reduce breast cancer risk in women past menopause who have osteoporosis (bone thinning) or are at high risk for breast cancer.

Aromatase inhibitors: Drugs such as anastrozole, letrozole, and exemestane are also being studied as breast cancer chemopreventive agents in post-menopausal women. These drugs are already being used to help prevent breast cancer recurrences. They work by blocking the production of small amounts of estrogen that post-menopausal women normally make. But they can also have side effects, such as causing joint pain and stiffness and bone loss, leading to a higher risk of osteoporosis. None of these drugs is approved for reducing the risk of developing breast cancer at this time.

Other drugs: Studies are looking at other drugs as well. For example, some studies have found that women who take aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen seem to have a lower risk of breast cancer. Studies are also looking to see if drugs called bisphosphonates may lower the risk of breast cancer. Bisphosphonates are drugs that are mainly used to treat osteoporosis, but they are also used to treat breast cancer that has spread to the bone. These, as well as several other drugs and dietary supplements, are being studied to see if they can lower breast cancer risk, but none is approved for reducing breast cancer risk at this time.

Many of the drugs mentioned here are discussed further in the section, "How is breast cancer treated?" For more information on the possible benefits and risks of chemopreventive drugs see our document, *Medicines to Reduce Breast Cancer Risk.*

Preventive surgery for women with very high breast cancer risk

For the few women who have a very high risk for breast cancer, surgery to remove the breasts or ovaries may be an option.

Preventive (prophylactic) mastectomy: Removing both breasts before cancer is diagnosed can greatly reduce the risk of breast cancer (by up to 97%). Some women diagnosed with cancer in one breast choose to have the other, healthy breast removed as well to prevent a second breast cancer. Breast removal does not completely prevent breast cancer because even a very careful surgeon will leave behind at least a few breast cells. The cells can go on to become cancerous. Some of the reasons for considering this type of surgery may include:

- Mutated BRCA genes found by genetic testing

- Previous cancer in one breast

- Strong family history (breast cancer in several close relatives)

- Lobular carcinoma in situ (LCIS) seen on biopsy

There is no way to know ahead of time whether this surgery will benefit a particular woman. Some women with BRCA mutations will develop breast cancer early in life, and have a very high risk of getting a second breast cancer. Prophylactic mastectomy before the cancer occurs might add many years to their lives. But while most women with

BRCA mutations develop breast cancer, some don't. These women would not benefit from the surgery, but they would still have to deal with its after- effects.

Second opinions are strongly recommended before any woman decides to have this surgery. The American Cancer Society Board of Directors has stated that "only very strong clinical and/or pathologic indications warrant doing this type of preventive operation." Nonetheless, after careful consideration, this might be the right choice for some women.

Prophylactic oophorectomy (ovary removal): Women with a BRCA mutation may reduce their risk of breast cancer by 50% or more by having their ovaries surgically removed before menopause. This is because the surgery removes the main sources of estrogen in the body (the ovaries).

This document is not about ovarian cancer, but it is important that women with a BRCA mutation recognize they also have a high risk of developing ovarian cancer. Most doctors recommend that women with BRCA mutations have their ovaries surgically removed once they finish having children to lower this risk.

Can breast cancer be found early?

Screening refers to tests and exams used to find a disease, like cancer, in people who do not have any symptoms. The goal of screening exams, such as mammograms, is to find cancers before they start to cause symptoms. Breast cancers that are found because they can be felt tend to be larger and are more likely to have already spread beyond the breast. In contrast, breast cancers found during screening exams are more likely to be small and still confined to the breast. The size of a breast cancer and how far it has spread are important factors in predicting the prognosis (outlook) for a woman with this disease.

Most doctors feel that early detection tests for breast cancer save many thousands of lives each year, and that many more lives could be saved if even more women and their health care providers took advantage of these tests. Following the American Cancer Society's guidelines for the early detection of breast cancer improves the chances that breast cancer can be diagnosed at an early stage and treated successfully.

American Cancer Society recommendations for early breast cancer detection

Women age 40 and older should have a screening mammogram every year and should continue to do so for as long as they are in good health.

- Current evidence supporting mammograms is even stronger than in the past. In particular, recent evidence has confirmed that mammograms offer substantial benefit for women in their 40s. Women can feel confident about the benefits associated with regular mammograms for finding cancer early. However, mammograms also have

limitations. A mammogram will miss some cancers, and it sometimes leads to follow up of findings that are not cancer, including biopsies.

- Women should be told about the benefits, limitations, and potential harms linked with regular screening. Mammograms can miss some cancers. But despite their limitations, they remain a very effective and valuable tool for decreasing suffering and death from breast cancer.

- Mammograms for older women should be based on the individual, her health, and other serious illnesses, such as congestive heart failure, end-stage renal disease, chronic obstructive pulmonary disease, and moderate-to-severe dementia. Age alone should not be the reason to stop having regular mammograms. As long as a woman is in good health and would be a candidate for treatment, she should continue to be screened with a mammogram.

Women in their 20s and 30s should have a clinical breast exam (CBE) as part of a periodic (regular) health exam by a health professional, at least every 3 years. After age 40, women should have a breast exam by a health professional every year.

- CBE is a complement to mammograms and an opportunity for women and their doctor or nurse to discuss changes in their breasts, early detection testing, and factors in the woman's history that might make her more likely to have breast cancer.

- There may be some benefit in having the CBE shortly before the mammogram. The exam should include instruction for the purpose of getting more familiar with your own breasts. Women should also be given information about the benefits and limitations of CBE and breast self exam (BSE). Breast cancer risk is very low for women in their 20s and gradually increases with age. Women should be told to promptly report any new breast symptoms to a health professional.

Breast self exam (BSE) is an option for women starting in their 20s. Women should be told about the benefits and limitations of BSE. Women should report any breast changes to their health professional right away.

- Research has shown that BSE plays a small role in finding breast cancer compared with finding a breast lump by chance or simply being aware of what is normal for each woman. Some women feel very comfortable doing BSE regularly (usually monthly after their period) which involves a systematic step-by-step approach to examining the look and feel of their breasts. Other women are more comfortable simply looking and feeling their breasts in a less systematic approach, such as while showering or getting dressed or doing an occasional thorough exam. Sometimes, women are so concerned about "doing it right" that they become stressed over the technique. Doing BSE regularly is one way for women to know how their breasts normally look and feel and to notice any changes. The goal, with or without BSE, is to report any breast changes to a doctor or nurse right away.

- Women who choose to do BSE should have their BSE technique reviewed during their physical exam by a health professional. It is okay for women to choose not to do BSE or not to do it on a regular schedule. However, by doing the exam regularly, you get to know how your breasts normally look and feel and you can more readily detect

any signs or symptoms if a change occurs, such as development of a lump or swelling, skin irritation or dimpling, nipple pain or retraction (turning inward), redness or scaliness of the nipple or breast skin, or a discharge other than breast milk. Should you notice any changes you should see your health care provider as soon as possible for evaluation. Remember that most of the time, however, these breast changes are not cancer.

Women at high risk (greater than 20% lifetime risk) should get an MRI and a mammogram every year. Women at moderately increased risk (15% to 20% lifetime risk) should talk with their doctors about the benefits and limitations of adding MRI screening to their yearly mammogram. Yearly MRI screening is not recommended for women whose lifetime risk of breast cancer is less than 15%.

Women at high risk include those who:

- Have a known BRCA1 or BRCA2 gene mutation

- Have a first-degree relative (parent, brother, sister, or child) with a BRCA1 or BRCA2 gene mutation, but have not had genetic testing themselves

- Have a lifetime risk of breast cancer of 20% to 25% or greater, according to risk assessment tools that are based mainly on family history (such as the Claus model - see below)

- Had radiation therapy to the chest when they were between the ages of 10 and 30 years

- Have Li-Fraumeni syndrome, Cowden syndrome, or hereditary diffuse gastric cancer, or have first-degree relatives with one of these syndromes

Women at moderately increased risk include those who:

- Have a lifetime risk of breast cancer of 15% to 20%, according to risk assessment tools that are based mainly on family history (see below)

- Have a personal history of breast cancer, ductal carcinoma in situ (DCIS), lobular carcinoma in situ (LCIS), atypical ductal hyperplasia (ADH), or atypical lobular hyperplasia (ALH)

- Have extremely dense breasts or unevenly dense breasts when viewed by mammograms

If MRI is used, it should be in addition to, not instead of, a screening mammogram. This is because while an MRI is a more sensitive test (it's more likely to detect cancer than a mammogram), it may still miss some cancers that a mammogram would detect.

For most women at high risk, screening with MRI and mammograms should begin at age 30 years and continue for as long as a woman is in good health. But because the evidence is limited regarding the best age at which to start screening, this decision should be based on shared decision making between patients and their health care providers, taking into account personal circumstances and preferences.

Several risk assessment tools, with names like the Gail model, the Claus model, and the Tyrer-Cuzick model, are available to help health professionals estimate a woman's breast cancer risk. These tools give approximate, rather than precise, estimates of breast cancer risk based on different combinations of risk factors and different data sets. As a result, they may give different risk estimates for the same woman. For example, the Gail model bases its risk estimates on certain personal risk factors, like age at menarche (first menstrual period) and history of prior breast biopsies, along with any history of breast cancer in first-degree relatives. The Claus model estimates risk based on family history of breast cancer in both first and second-degree relatives. These 2 models could easily give different estimates using the same data. Results obtained from any of the risk assessment tools should be discussed by a woman and her doctor when being used to decide whether to start MRI screening.

It is recommended that women who get screening MRI do so at a facility that can do an MRI-guided breast biopsy at the same time if needed. Otherwise, the woman will have to have a second MRI exam at another facility at the time of biopsy.

There is no evidence right now that MRI will be an effective screening tool for women at average risk. MRI is more sensitive than mammograms, but it also has a higher false-positive rate (it is more likely to find something that turns out not to be cancer). This would lead to unneeded biopsies and other tests in many of these women.

The American Cancer Society believes the use of mammograms, MRI (in women at high risk), clinical breast exams, and finding and reporting breast changes early, according to the recommendations outlined above, offers women the best chance to reduce their risk of dying from breast cancer. This combined approach is clearly better than any one exam or test alone. Without question, breast physical exam without a mammogram would miss the opportunity to detect many breast cancers that are too small for a woman or her doctor to feel but can be seen on mammograms. Although mammograms are a sensitive screening method, a small percentage of breast cancers do not show up on mammograms but can be felt by a woman or her doctors. For women at high risk of breast cancer, like those with BRCA gene mutations or a strong family history, both MRI and mammogram exams of the breast are recommended.

Mammograms

A mammogram is an x-ray of the breast. A diagnostic mammogram is used to diagnose breast disease in women who have breast symptoms or an abnormal result on a screening mammogram. Screening mammograms are used to look for breast disease in women who are asymptomatic; that is, they appear to have no breast problems. Screening mammograms usually take 2 views (x-ray pictures taken from different angles) of each breast. For some patients, such as women with breast implants, more pictures may be needed to include as much breast tissue as possible. Women who are breast-feeding can still get mammograms, but these are probably not quite as accurate because the breast tissue tends to be dense.

Breast x-rays have been done for more than 70 years, but the modern mammogram has only existed since 1969. That was the first year x-ray units specifically for breast imaging

were available. Modern mammogram equipment designed for breast x-rays uses very low levels of radiation, usually a dose of about 0.1 to 0.2 rads per picture (a rad is a measure of radiation dose).

Strict guidelines ensure that mammogram equipment is safe and uses the lowest dose of radiation possible. Many people are concerned about the exposure to x-rays, but the level of radiation used in modern mammograms does not significantly increase the risk for breast cancer.

To put dose into perspective, if a woman with breast cancer is treated with radiation, she will receive around 5,000 rads. If she had yearly mammograms beginning at age 40 and continuing until she was 90, she will have received 20 to 40 rads.

For a mammogram, the breast is pressed between 2 plates to flatten and spread the tissue. This may be uncomfortable for a moment, but it is necessary to produce a good, readable mammogram. The compression only lasts a few seconds. The entire procedure for a screening mammogram takes about 20 minutes. This procedure produces a black and white image of the breast tissue either on a large sheet of film or as a digital computer image that is read, or interpreted, by a radiologist (a doctor trained to interpret images from x-rays, ultrasound, MRI, and related tests).

Some advances in technology, like digital mammography, may help doctors read mammograms more accurately. They are described in the section, "How is breast cancer diagnosed?"

What the doctor looks for on your mammogram

The doctor reading the films will look for several types of changes:

Calcifications are tiny mineral deposits within the breast tissue, which look like small white spots on the films. They may or may not be caused by cancer. There are 2 types of calcifications:

- Macrocalcifications are coarse (larger) calcium deposits that are most likely changes in the breasts caused by aging of the breast arteries, old injuries, or inflammation. These deposits are related to non-cancerous conditions and do not require a biopsy. Macrocalcifications are found in about half the women over 50, and in about 1 of 10 women under 50.

- Microcalcifications are tiny specks of calcium in the breast. They may appear alone or in clusters. Microcalcifications seen on a mammogram are of more concern, but still usually do not mean that cancer is present. The shape and layout of microcalcifications help the radiologist judge how likely it is that cancer is present. If the calcifications look suspicious for cancer, a biopsy will be done.

A *mass*, which may occur with or without calcifications, is another important change seen on mammograms. Masses can be many things, including cysts (non-cancerous, fluid-filled sacs) and non-cancerous solid tumors (such as fibroadenomas), but they could also be cancer. Masses that are not cysts usually need to be biopsied.

- A cyst and a tumor can feel alike on a physical exam. They can also look the same on a mammogram. To confirm that a mass is really a cyst, a breast ultrasound is often done. Another option is to remove (aspirate) the fluid from the cyst with a thin, hollow needle.

- If a mass is not a simple cyst (that is, if it is at least partly solid), then you may need to have more imaging tests. Some masses can be watched with periodic mammograms, while others may need a biopsy. The size, shape, and margins (edges) of the mass help the radiologist determine if cancer is present.

Having your previous mammograms available for the radiologist is very important. They can be helpful to show that a mass or calcification has not changed for many years. This would mean that it is probably a benign condition and a biopsy is not needed.

Limitations of mammograms

A mammogram cannot prove that an abnormal area is cancer. To confirm whether cancer is present, a small amount of tissue must be removed and looked at under a microscope. This procedure, called a *biopsy*, is described in the section, "How is breast cancer diagnosed?"

You should also be aware that mammograms are done to find breast cancer that cannot be felt. If you have a breast lump, you should have it checked by your doctor and consider having it biopsied even if your mammogram result is normal.

For some women, such as those with breast implants, additional pictures may be needed. Breast implants make it harder to see breast tissue on standard mammograms, but additional x-ray pictures with implant displacement and compression views can be used to more completely examine the breast tissue.

Mammograms are not perfect at finding breast cancer. They do not work as well in younger women, usually because their breasts are dense, and can hide a tumor. This may also be true for pregnant women and women who are breast-feeding. Since most breast cancers occur in older women, this is usually not a major concern.

However, this can be a problem for young women who are at high risk for breast cancer (due to gene mutations, a strong family history of breast cancer, or other factors) because they often develop breast cancer at a younger age. For this reason, the American Cancer Society now recommends MRI scans in addition to mammograms for screening in these women. (MRI scans are described below.)

For more information on these tests, also see the section, "How is breast cancer diagnosed?" and our document, *Mammograms and Other Breast Imaging Procedures*.

What to expect when you have a mammogram

- To have a mammogram you must undress above the waist. The facility will give you a wrap to wear.

- A technologist will be there to position your breasts for the mammogram. Most technologists are women. You and the technologist are the only ones in the room during the mammogram.

- To get a high-quality mammogram picture with excellent image quality, it is necessary to flatten the breast slightly. The technologist places the breast on the mammogram machine's lower plate, which is made of metal and has a drawer to hold the x-ray film or the camera to produce a digital image. The upper plate, made of plastic, is lowered to compress the breast for a few seconds while the technician takes a picture.

- The whole procedure takes about 20 minutes. The actual breast compression only lasts a few seconds.

- You will feel some discomfort when your breasts are compressed, and for some women compression can be painful. Try not to schedule a mammogram when your breasts are likely to be tender, as they may be just before or during your period.

- All mammogram facilities are now required to send your results to you within 30 days. Generally, you will be contacted within 5 working days if there is a problem with the mammogram.

- Only 2 to 4 mammograms of every 1,000 lead to a diagnosis of cancer. About 10% of women who have a mammogram will require more tests, and the majority will only need an additional mammogram. Don't panic if this happens to you. Only 8% to 10% of those women will need a biopsy, and most (80%) of those biopsies will not be cancer.

If you are a woman aged 40 or over, you should get a mammogram every year. You can schedule the next one while you're at the facility and/or request a reminder.

Tips for having a mammogram

The following are useful suggestions for making sure that you will receive a quality mammogram:

- If it is not posted visibly near the receptionist's desk, ask to see the FDA certificate that is issued to all facilities that offer mammography. The FDA requires that all facilities meet high professional standards of safety and quality in order to be a provider of mammography services. A facility may not provide mammography without certification.

- Use a facility that either specializes in mammography or does many mammograms a day.

- If you are satisfied that the facility is of high quality, continue to go there on a regular basis so that your mammograms can be compared from year to year.

- If you are going to a facility for the first time, bring a list of the places, dates of mammograms, biopsies, or other breast treatments you have had before.

- If you have had mammograms at another facility, you should make every attempt to get those mammograms to bring with you to the new facility (or have them sent there) so that they can be compared to the new ones.

- On the day of the exam don't wear deodorant or antiperspirant. Some of these contain substances that can interfere with the reading of the mammogram by appearing on the x-ray film as white spots.

- You may find it easier to wear a skirt or pants, so that you'll only need to remove your blouse for the exam.

- Schedule your mammogram when your breasts are not tender or swollen to help reduce discomfort and to ensure a good picture. Try to avoid the week just before your period.

- Always describe any breast symptoms or problems that you are having to the technologist who is doing the mammogram. Be prepared to describe any medical history that could affect your breast cancer risk -- such as surgery, hormone use, or family or personal history of breast cancer. Discuss any new findings or problems in your breasts with your doctor or nurse before having a mammogram.

- If you do not hear from your doctor within 10 days, do not assume that your mammogram was normal -- call your doctor or the facility.

Help with mammogram costs

Medicare, Medicaid, and most private health insurance plans cover mammogram costs or a percentage of them. Low-cost mammograms are available in most communities. Call us at 1-800-227-2345 for information about facilities in your area.

Breast cancer screening is now more available to medically underserved women through the National Breast and Cervical Cancer Early Detection Program (NBCCEDP). This program provides breast and cervical cancer early detection testing to women without health insurance for free or at very low cost. Although the program is administered within each state, the Centers for Disease Control and Prevention (CDC) provide matching funds and support to each state program. Each state's Department of Health has information on how to contact the nearest program.

The program is only designed to provide screening. But if a cancer is discovered, it will cover further diagnostic testing and a surgical consultation.

The Breast and Cervical Cancer Prevention and Treatment Act gives states Medicaid funds to pay for treating breast and cervical cancers that are detected through the NBCCEDP. This helps women focus their energies on fighting their disease, instead of worrying about how to pay for treatment. All states participate in this program.

To learn more about these programs, please contact the CDC at 1-800-CDC INFO (1-800-232-4636) or online at www.cdc.gov/cancer/nbccedp.

Clinical breast exam

A clinical breast exam (CBE) is an exam of your breasts by a health care professional, such as a doctor, nurse practitioner, nurse, or doctor's assistant. For this exam, you undress from the waist up. The health care professional will first look at your breasts for abnormalities in size or shape, or changes in the skin of the breasts or nipple. Then, using the pads of the fingers, the examiner will gently feel (palpate) your breasts.

Special attention will be given to the shape and texture of the breasts, location of any lumps, and whether such lumps are attached to the skin or to deeper tissues. The area under both arms will also be examined.

The CBE is a good time for women who don't know how to examine their breasts to learn the proper technique from their health care professionals. Ask your doctor or nurse to teach you and watch your technique.

Breast awareness and self exam

Beginning in their 20s, women should be told about the benefits and limitations of breast self-exam (BSE). Women should know how their breasts normally look and feel and report any new breast changes to a health professional as soon as they are found. Finding a breast change does not necessarily mean there is a cancer.

A woman can notice changes by being aware of how her breasts normally look and feel and by feeling her breasts for changes (breast awareness), or by choosing to use a step-by-step approach (see below) and using a specific schedule to examine her breasts.

If you choose to do BSE, the information below is a step-by-step approach for the exam. The best time for a woman to examine her breasts is when the breasts are not tender or swollen. Women who examine their breasts should have their technique reviewed during their periodic health exams by their health care professional.

Women with breast implants can do BSE, too. It may be helpful to have the surgeon help identify the edges of the implant so that you know what you are feeling. There is some thought that the implants push out the breast tissue and may actually make it easier to examine. Women who are pregnant or breast-feeding can also choose to examine their breasts regularly.

It is acceptable for women to choose not to do BSE or to do BSE once in a while. Women who choose not to do BSE should still be aware of the normal look and feel of their breasts and report any changes to their doctor right away.
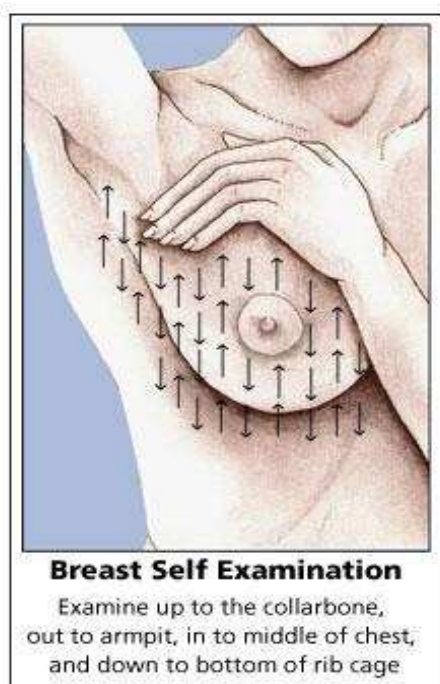
How to examine your breasts

- Lie down and place your right arm behind your head. The exam is done while lying down, not standing up. This is because when lying down the breast tissue spreads evenly over the chest wall and is as thin as possible, making it much easier to feel all the breast tissue.

- Use the finger pads of the 3 middle fingers on your left hand to feel for lumps in the right breast. Use overlapping dime-sized circular motions of the finger pads to feel the breast tissue.
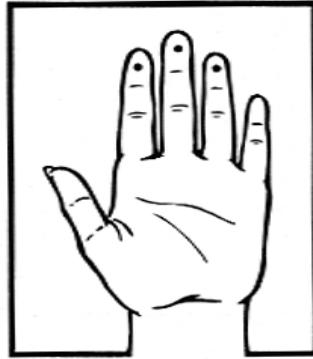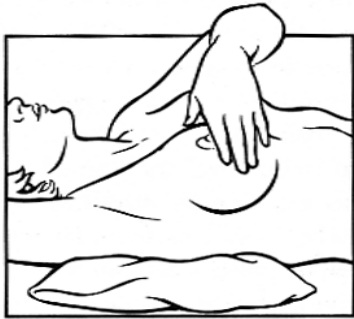
- Use 3 different levels of pressure to feel all the breast tissue. Light pressure is needed to feel the tissue closest to the skin; medium pressure to feel a little deeper; and firm pressure to feel the tissue closest to the chest and ribs. It is normal to feel a firm ridge in the lower curve of each breast, but you should tell your doctor if you feel anything else out of the ordinary. If you're not sure how hard to press, talk with your doctor or nurse. Use each pressure level to feel the breast tissue before moving on to the next spot.

- Move around the breast in an up and down pattern starting at an imaginary line drawn straight down your side from the underarm and moving across the breast to the middle of the chest bone (sternum or breastbone). Be sure to check the entire breast area going down until you feel only ribs and up to the neck or collar bone (clavicle).

Breast Self Examination

Examine up to the collarbone,
out to armpit, in to middle of chest,
and down to bottom of rib cage

- There is some evidence to suggest that the up-and-down pattern (sometimes called the vertical pattern) is the most effective pattern for covering the entire breast, without missing any breast tissue.

- Repeat the exam on your left breast, putting your left arm behind your head and using the finger pads of your right hand to do the exam.

- While standing in front of a mirror with your hands pressing firmly down on your hips, look at your breasts for any changes of size, shape, contour, or dimpling, or redness or scaliness of the nipple or breast skin. (The pressing down on the hips position contracts the chest wall muscles and enhances any breast changes.)

- Examine each underarm while sitting up or standing and with your arm only slightly raised so you can easily feel in this area. Raising your arm straight up tightens the tissue in this area and makes it harder to examine.

This procedure for doing breast self exam is different from previous recommendations. These changes represent an extensive review of the medical literature and input from an expert advisory group. There is evidence that this position (lying down), the area felt, pattern of coverage of the breast, and use of different amounts of pressure increase a woman's ability to find abnormal areas.

Magnetic resonance imaging (MRI)

For certain women at high risk for breast cancer, screening MRI is recommended along with a yearly mammogram. It is not generally recommended as a screening tool by itself, because although it is a sensitive test, it may still miss some cancers that mammograms would detect.

MRI scans use magnets and radio waves (instead of x-rays) to produce very detailed, cross-sectional images of the body. The most useful MRI exams for breast imaging use a contrast material (gadolinium) that is injected into a vein in the arm before or during the exam. This improves the ability of the MRI to clearly show breast tissue details. (For more details on how an MRI test is done, see the section, " How is breast cancer diagnosed?")

MRI is more sensitive in detecting cancers than mammograms, but it also has a higher false-positive rate (where the test finds something that turns out not to be cancer), which results in more recalls and biopsies. This is why it is not recommended as a screening test for women at average risk of breast cancer, as it would result in unneeded biopsies and other tests in a large portion of these women.

Just as mammography uses x-ray machines that are specially designed to image the breasts, breast MRI also requires special equipment. Breast MRI machines produce higher quality images than MRI machines designed for head, chest, or abdominal scanning. However, many hospitals and imaging centers do not have dedicated breast MRI equipment available. It is important that screening MRIs be done at facilities that can perform an MRI-guided breast biopsy. Otherwise, the entire scan will need to be repeated at another facility when the biopsy is done.

MRI is more expensive than mammography. Most major insurance companies will likely pay for these screening tests if a woman can be shown to be at high risk, but it's not yet clear if all companies will do so. At this time there are concerns about costs of and limited access to high-quality MRI breast screening services for women at high risk of breast cancer.

How is breast cancer diagnosed?

Breast cancer is sometimes found after symptoms appear, but many women with early breast cancer have no symptoms. This is why getting the recommended screening tests (as described in the section, "Can breast cancer be found early?") before any symptoms develop is so important.

If something suspicious is found during a screening exam, or if you have any of the symptoms of breast cancer described below, your doctor will use one or more methods to find out if the disease is present. If cancer is found, other tests will be done to determine the stage (extent) of the cancer.

Signs and symptoms

Widespread use of screening mammograms has increased the number of breast cancers found before they cause any symptoms, but some breast cancers are not found by mammogram, either because the test was not done or because, even under ideal conditions, mammograms do not find every breast cancer.

The most common sign of breast cancer is a new lump or mass. A painless, hard mass that has irregular edges is more likely to be cancerous, but breast cancers can be tender,

soft, or rounded. For this reason, it is important that any new breast mass or lump be checked by a health care professional experienced in diagnosing breast diseases.

Other possible signs of breast cancer include:

- Swelling of all or part of a breast (even if no distinct lump is felt)

- Skin irritation or dimpling

- Breast or nipple pain

- Nipple retraction (turning inward)

- Redness, scaliness, or thickening of the nipple or breast skin

- Nipple discharge (other than breast milk)

Sometimes a breast cancer can spread to underarm lymph nodes and cause a lump or swelling there, even before the original tumor in the breast tissue is large enough to be felt.

Medical history and physical exam

If you have any signs or symptoms that might be due to breast cancer, be sure to see your doctor as soon as possible. Your doctor will ask you questions about your symptoms, any other health problems, and possible risk factors for benign breast conditions or breast cancer.

Your breasts will be thoroughly examined for any lumps or suspicious areas and to feel their texture, size, and relationship to the skin and chest muscles. Any changes in the nipples or the skin of your breasts will be noted. The lymph nodes in the armpit and above the collarbones may be palpated (felt), because enlargement or firmness of these lymph nodes might indicate spread of breast cancer. Your doctor may also probably do a complete physical exam to judge your general health and whether there is any evidence of cancer that may have spread.

If breast symptoms and/or the results of your physical exam suggest breast cancer might be present, more tests will likely be done. These might include imaging tests, looking at samples of nipple discharge, or doing biopsies of suspicious areas.

Imaging tests used to evaluate breast disease

Imaging tests use x-rays, magnetic fields, sound waves, or radioactive substances to create pictures of the inside of your body. Imaging tests may be done for a number of reasons, including to help find out whether a suspicious area might be cancerous, to learn how far cancer may have spread, and to help determine if treatment is working.

Diagnostic mammograms

Mammograms are mostly used for screening, but they can also be used to examine the breast of a woman who has a breast problem. This can be a breast mass, nipple discharge, or an abnormality that was found on a screening mammogram. In some cases, special images known as *cone views with magnification* are used to make a small area of abnormal breast tissue easier to evaluate.

A diagnostic mammogram can show:

- That the abnormality is not worrisome at all. In these cases the woman can usually return to having routine yearly mammograms.

- That a lesion (area of abnormal tissue) has a high likelihood of being benign (not cancer). In these cases, it is common to ask the woman to come back sooner than usual for her next mammogram, usually in 4 to 6 months.

- That the lesion is more suspicious, and a biopsy is needed to tell if it is cancer.

Even if the mammograms show no tumor, if you or your doctor can feel a lump, a biopsy is usually needed to make sure it isn't cancer. One exception would be if an ultrasound exam finds that the lump is a simple cyst (a fluid-filled sac), which is very unlikely to be cancerous.

Digital mammograms: A digital mammogram (also known as a *full-field digital mammogram,* or *FFDM*) is like a standard mammogram in that x-rays are used to produce an image of your breast. The differences are in the way the image is recorded, viewed by the doctor, and stored. Standard mammograms are recorded on large sheets of photographic film. Digital mammograms are recorded and stored on a computer. After the exam, the doctor can look at them on a computer screen and adjust the image size, brightness, or contrast to see certain areas more clearly. Digital images can also be sent electronically to another site for a remote consult with breast specialists. Many centers do not offer the digital option, but it is becoming more widely available with time.

Because digital mammograms cost more than standard mammograms, studies are now looking at which form of mammogram will benefit more women in the long run. Some studies have found that women who have a FFDM have to return less often for additional imaging tests because of inconclusive areas on the original mammogram. A recent large study found that a FFDM was more accurate in finding cancers in women younger than 50 and in women with dense breast tissue, although the rates of inconclusive results were similar between FFDM and film mammograms. It is important to remember that a standard film mammogram also is effective for these groups of women, and that they should not miss their regular mammogram if a digital mammogram is not available.

Computer-aided detection and diagnosis (CAD): Over the past 2 decades, computer-aided detection and diagnosis (CAD) has been developed to help radiologists detect suspicious changes on mammograms. This can be done with standard film mammograms or with digital mammograms.

Computers can help doctors identify abnormal areas on a mammogram by acting as a second set of eyes. For standard mammograms, the film is fed into a machine which converts the image into a digital signal that is then analyzed by the computer. Alternatively, the technology can be applied to a digital mammogram. The computer then displays the image on a video screen, with markers pointing to areas that the radiologist should check especially closely.

It's not yet clear how useful CAD is. Some doctors find it helpful, but a recent, large study found it did not significantly improve the accuracy of breast cancer detection. It did, however, increase the number of women who needed to have breast biopsies. Further research is needed.

Magnetic resonance imaging (MRI) of the breast

MRI scans use radio waves and strong magnets instead of x-rays. The energy from the radio waves is absorbed and then released in a pattern formed by the type of body tissue and by certain diseases. A computer translates the pattern into a very detailed image of parts of the body. A contrast liquid called gadolinium is often injected into a vein before or during the scan to show details better.

MRI scans can take a long time -- often up to an hour. You have to lie inside a narrow tube, which is confining and may upset people with claustrophobia (a fear of enclosed spaces). The machine also makes loud buzzing and clicking noises that you may find disturbing. Some places will give you headphones with music to block this out. MRIs are also expensive, although insurance plans generally pay for them in some situations, such as once cancer is diagnosed.

MRI machines are quite common, but they need to be specially adapted to look at the breast. It's important that MRI scans of the breast be done on one of these specially adapted machines.

MRI can be used along with mammograms for screening women who have a high risk of developing breast cancer, or it can be used to better examine suspicious areas found by a mammogram. MRI is also used for women who have been diagnosed with breast cancer to better determine the actual size of the cancer and to look for any other cancers in the breast.

If an abnormal area in the breast is found, it can often be biopsied using an MRI for guidance. This is discussed in more detail in the "Biopsy" section.

Breast ultrasound

Ultrasound, also known as *sonography*, uses sound waves to outline a part of the body. For this test, a small, microphone-like instrument called a transducer is placed on the skin (which is often first lubricated with ultrasound gel). It emits sound waves and picks up the echoes as they bounce off body tissues. The echoes are converted by a computer into a black and white image that is displayed on a computer screen. This test is painless and does not expose you to radiation.

Ultrasound has become a valuable tool to use along with mammography because it is widely available and less expensive than other options, such as MRI. The use of ultrasound instead of mammograms for breast cancer screening is not recommended. Usually, breast ultrasound is used to target a specific area of concern found on the mammogram. Ultrasound helps distinguish between cysts (fluid-filled sacs) and solid masses and sometimes can help tell the difference between benign and cancerous tumors.

Ultrasound may be most helpful in women with very dense breasts. Clinical trials are now looking at the benefits and risks of adding breast ultrasound to screening mammograms in women with dense breasts and a higher risk of breast cancer.

Ductogram

This test, also called a *galactogram*, sometimes helps determine the cause of nipple discharge. In this test a very thin plastic tube is placed into the opening of the duct in the nipple that the discharge is coming from. A small amount of contrast medium is injected, which outlines the shape of the duct on an x-ray image and shows if there is a mass inside the duct.

Newer imaging tests

Newer tests like scintimammography and tomosynthesis are not used commonly and are still being studied to determine their usefulness. They are described in the section, "What's new in breast cancer research and treatment?"

Other tests

These tests may be done for the purposes of research, but they have not yet been found to be helpful in diagnosing breast cancer in most women.

Nipple discharge exam

If you are having nipple discharge, some of the fluid may be collected and looked at under a microscope to see if any cancer cells are in it. Most nipple discharges or secretions are not cancer. In general, if the secretion appears milky or clear green, cancer is very unlikely. If the discharge is red or red-brown, suggesting that it contains blood, it might possibly be caused by cancer, although an injury, infection, or benign tumors are more likely causes.

Even when no cancer cells are found in a nipple discharge, it is not possible to say for certain that a breast cancer is not there. If a patient has a suspicious mass, it will be necessary to biopsy the mass, even if the nipple discharge does not contain cancer cells.

Ductal lavage and nipple aspiration

Ductal lavage is an experimental test developed for women who have no symptoms of breast cancer but are at very high risk for the disease. It is not a test to screen for or

diagnose breast cancer, but it may help give a more accurate picture of a woman's risk of developing it.

Ductal lavage can be done in a doctor's office or an outpatient facility. An anesthetic cream is applied to numb the nipple area. Gentle suction is then used to help draw tiny amounts of fluid from the milk ducts up to the nipple surface, which helps locate the ducts' natural openings. A tiny tube (called a *catheter*) is then inserted into a duct opening. Saline (salt water) is slowly infused into the catheter to gently rinse the duct and collect cells. The ductal fluid is withdrawn through the catheter and sent to a lab, where the cells are looked at under a microscope.

Ductal lavage is not considered appropriate for women who aren't at high risk for breast cancer. It is not clear if it will ever be useful. The test has not been shown to detect cancer early. It is more likely to be helpful as a test of cancer risk rather than as a screening test for cancer. More studies are needed to better define the usefulness of this test.

Nipple aspiration also looks for abnormal cells developing in the ducts, but is much simpler, because nothing is inserted into the breast. The device for nipple aspiration uses small cups that are placed on the woman's breasts. The device warms the breasts, gently compresses them, and applies light suction to bring nipple fluid to the surface of the breast. The nipple fluid is then collected and sent to a lab for analysis. As with ductal lavage, the procedure may be useful as a test of cancer risk but is not appropriate as a screening test for cancer. The test has not been shown to detect cancer early.

Biopsy

During a biopsy, the doctor removes a sample of the suspicious area to be looked at under a microscope. A biopsy is done when mammograms, other imaging tests, or the physical exam finds a breast change (or abnormality) that is possibly cancer. A biopsy is the only way to tell if cancer is really present.

There are several types of biopsies, such as fine needle aspiration biopsy, core (large needle) biopsy, and surgical biopsy. Each has its pros and cons. The choice of which to use depends on your specific situation. Some of the factors your doctor will consider include how suspicious the lesion appears, how large it is, where in the breast it is located, how many lesions are present, other medical problems you may have, and your personal preferences. You might want to discuss the pros and cons of different biopsy types with your doctor.

Fine needle aspiration biopsy

In a fine needle aspiration (FNA) biopsy, the doctor uses a very thin, hollow needle attached to a syringe to withdraw (aspirate) a small amount of tissue from a suspicious area, which is then looked at under a microscope. The needle used for an FNA biopsy is thinner than the ones used for blood tests.

If the area to be biopsied can be felt, the needle can be guided into the area of the breast change while the doctor is feeling (palpating) it.

If the lump can't be felt easily, the doctor might use ultrasound to watch the needle on a screen as it moves toward and into the mass.

A local anesthetic (numbing medicine) may or may not be used. Because such a thin needle is used for the biopsy, the process of getting the anesthetic may actually be more uncomfortable than the biopsy itself.

Once the needle is in place, fluid is drawn out. If the fluid is clear, the lump is probably a benign cyst. Bloody or cloudy fluid can mean either a benign cyst or, very rarely, a cancer. If the lump is solid, small tissue fragments are drawn out. A pathologist will look at the biopsy tissue or fluid under a microscope to determine if it is cancerous.

An FNA biopsy is the easiest type of biopsy to have, but it has some disadvantages. It can sometimes miss a cancer if the needle is not placed among the cancer cells. And even if cancer cells are found, it is usually not possible to determine if the cancer is invasive. In some cases there may not be enough cells to perform some of the other lab tests that are routinely done on breast cancer specimens. If the FNA biopsy does not provide a clear diagnosis, or your doctor is still suspicious, a second biopsy or a different type of biopsy should be done.

Core needle biopsy

A core biopsy uses a larger needle to sample breast changes felt by the doctor or pinpointed by ultrasound or mammogram. (When mammograms taken from different angles are used to pinpoint the biopsy site, this is known as a stereotactic core needle biopsy.) In some centers, the biopsy can be guided by an MRI scan.

The needle used in core biopsies is larger than that used in FNA. It removes a small cylinder (core) of tissue (about 1/16- to 1/8-inch in diameter and ½-inch long) from a breast abnormality. Several cores are often removed. The biopsy is done using local anesthesia (where you are awake but the area is numbed) in an outpatient setting.

Because it removes larger pieces of tissue, a core needle biopsy is more likely than an FNAB to provide a clear diagnosis, although it may still miss some cancers.

Vacuum-assisted biopsies

Vacuum-assisted biopsies can be done with systems such as the Mammotome® or ATEC® (Automated Tissue Excision and Collection). For these procedures the skin is numbed and a small incision (about ¼ inch) is made. A hollow probe is inserted through the incision into the abnormal area of breast tissue. The probe can be guided into place using x-rays or ultrasound (or MRI in the case of the ATEC system). A cylinder of tissue is then suctioned in through a hole in the side the probe, and a rotating knife within the probe cuts the tissue sample from the rest of the breast. Several samples can be taken from the same incision. Vacuum-assisted biopsies are done as an outpatient procedure.

No stitches are needed, and there is minimal scarring. This method usually removes more tissue than core biopsies.

Surgical (open) biopsy

Sometimes, surgery is needed to remove all or part of the lump for microscopic examination. This is referred to as a surgical biopsy or an open biopsy. Usually this is an excisional biopsy, where the surgeon removes the entire mass or abnormal area, as well as a surrounding margin of normal-appearing breast tissue. If the mass is too large to be removed easily, an incisional biopsy may be done instead. In this type of biopsy only part of the mass is removed. In rare cases, this type of biopsy can be done in the doctor's office, but it is more commonly done in the hospital's outpatient department under a local anesthesia (where you are awake, but your breast is numbed). You may also be given medicine to make you drowsy. This type of biopsy can also be done under general anesthesia, (you are asleep).

During a surgical breast biopsy the surgeon may use a procedure called *stereotactic wire localization* if there is a small lump that is hard to locate by touch or if an area looks suspicious on the x-ray but cannot be felt. After the area is numbed with local anesthetic, a thin hollow needle is placed into the breast, and x-ray views are used to guide the needle to the suspicious area. Once the tip of the needle is in the right spot, a thin wire is inserted through the center of the needle. A small hook at the end of the wire keeps it in place. The hollow needle is then removed. The surgeon can then use the wire as a guide to the abnormal area to be removed. The surgical specimen is sent to the lab to be looked at under a microscope (see below).

This type of biopsy is more involved than an FNA biopsy or a core needle biopsy, typically requires several stitches and may leave a scar. Core needle biopsy is usually enough to make a diagnosis, but sometimes an open biopsy may be needed depending on where the lesion is, or if a core biopsy is not conclusive.

Lymph node dissection and sentinel lymph node biopsy

These procedures are done specifically to look for cancer in the lymph nodes. They are described in more detail in the section, "How is breast cancer treated?"

Laboratory examination of breast cancer tissue

The biopsy samples of breast tissue are looked at in the lab to determine whether breast cancer is present and if so, what type it is. The lab may also perform certain tests that can help determine how quickly a cancer is likely to grow and (to some extent) what treatments are likely to be effective. Sometimes these tests aren't done on the biopsy sample, but instead they are performed on the whole cancer specimen when it is removed by either lumpectomy or mastectomy.

If a benign condition is diagnosed, you will need no further treatment. Still, it is important to find out from your doctor if the benign condition places you at higher risk for breast cancer in the future and what type of follow-up you might need.

If the diagnosis is cancer, there should be time for you to learn about the disease and to discuss treatment options with your cancer care team, friends, and family. It is usually not necessary to rush into treatment. You may want to get a second opinion before deciding on what treatment is best for you.

Type of breast cancer

The tissue removed during the biopsy (or during surgery) is first looked at under a microscope to see if cancer is present and whether it is in situ (not invasive) or invasive. The biopsy is also used to determine the cancer's type. The different types of breast cancer are defined in the section, "What is breast cancer?"

The most common types, invasive ductal and invasive lobular cancer, generally are treated in the same way.

Breast cancer grade

A pathologist also assigns a grade to the cancer, which is based on how closely the biopsy sample resembles normal breast tissue. The grade helps predict a woman's prognosis. In general, a lower grade number indicates a slower-growing cancer that is less likely to spread, while a higher number indicates a faster-growing cancer that is more likely to spread. The tumor grade is one factor in deciding the need for further treatment after surgery.

Histologic tumor grade (sometimes called the *Bloom-Richardson grade*, *Scarff-Bloom-Richardson grade*, or *Elston-Ellis grade*) is based on the arrangement of the cells in relation to each other: whether they form tubules; how closely they resemble normal breast cells (nuclear grade); and how many of the cancer cells are in the process of dividing (mitotic count). This system of grading is used for invasive cancers but not for in situ cancers.

- Grade 1 (well differentiated) cancers have relatively normal-looking cells that do not appear to be growing rapidly and are arranged in small tubules.

- Grade 2 (moderately differentiated) cancers have features between grades 1 and 3.

- Grade 3 (poorly differentiated) cancers, the highest grade, lack normal features and tend to grow and spread more aggressively.

Ductal carcinoma in situ (DCIS) is sometimes given a nuclear grade, which describes how abnormal the cancer cells appear. The presence or absence of necrosis (areas of dead or degenerating cancer cells), which might indicate a more aggressive cancer, is also noted. Other factors important in determining the prognosis for DCIS include the surgical margin (how close the cancer is to the edge of the specimen) and the size (amount of breast tissue affected by DCIS). In situ cancers with high nuclear grade, necrosis, cancer

at or near the edge of the sample, or large areas of DCIS are more likely to come back after treatment.

Estrogen receptor (ER) and progesterone receptor (PR) status

Receptors are proteins on the outside surfaces of cells that can attach to certain substances, such as hormones, that circulate in the blood. Normal breast cells and some breast cancer cells have receptors that attach to estrogen and progesterone. These 2 hormones often fuel the growth of breast cancer cells.

An important step in evaluating a breast cancer is to test a portion of the cancer removed during the biopsy (or surgery) to see if they have estrogen and progesterone receptors. Cancer cells may contain neither, one, or both of these receptors. Breast cancers that contain estrogen receptors are often referred to as *ER-positive* (or ER+) cancers, while those containing progesterone receptors are called *PR-positive* (or PR+) cancers. Women with hormone receptor–positive cancers tend to have a better prognosis and are much more likely to respond to hormone therapy than women with cancers without these receptors.

All breast cancers, with the exception of lobular carcinoma in situ (LCIS), should be tested for these hormone receptors when they have the breast biopsy or surgery. About 2 of 3 breast cancers contain at least one of these receptors. This percentage is higher in older women than in younger ones.

HER2/neu status

About 1 of 5 breast cancers have too much of a growth-promoting protein called HER2/neu (often just shortened to HER2). The HER2/neu gene instructs the cells to make this protein. Tumors with increased levels of HER2/neu are referred to as *HER2-positive*.

Women with HER2-positive breast cancers have too many copies of the HER2/neu gene, resulting in greater than normal amounts of the HER2/neu protein. These cancers tend to grow and spread more aggressively than other breast cancers.

All newly diagnosed breast cancers should be tested for HER2/neu because HER2-positive cancers are much more likely to benefit from treatment with drugs that target the HER2/neu protein, such as trastuzumab (Herceptin®) and lapatinib (Tykerb®). See the section, "How is breast cancer treated?" for more information on these drugs.

Testing of the biopsy or surgery sample is usually done in one of two ways:

- Immunohistochemistry (IHC): In this test, special antibodies that identify the HER2/neu protein are applied to the sample, which cause cells to change color if many copies are present. This color change can be seen under a microscope. The test results are reported as 0, 1+, 2+, or 3+.

- Fluorescent in situ hybridization (FISH): This test uses fluorescent pieces of DNA that specifically stick to copies of the HER2/neu gene in cells, which can then be counted under a special microscope.

Many breast cancer specialists feel the FISH test is more accurate than IHC. However, it is more expensive and takes longer to get the results. Often the IHC test is used first. If the results are 1+ (or 0), the cancer is considered HER2-negative. People with HER2-negative tumors are not treated with drugs (like trastuzumab) that target HER2. If the test comes back 3+, the cancer is HER2-positive. Patients with HER2-positive tumors may be treated with drugs like trastuzumab. When the result is 2+, the HER2 status of the tumor is not clear. This often leads to testing the tumor with FISH. Newer test methods are now becoming available as well (see "What's new in breast cancer research and treatment?").

Tests of ploidy and cell proliferation rate

The ploidy of cancer cells refers to the amount of DNA they contain. If there's a normal amount of DNA in the cells, they are said to be diploid. If the amount is abnormal, then the cells are described as aneuploid. Tests of ploidy may help determine prognosis, but they rarely change treatment and are considered optional. They are not usually recommended as part of a routine breast cancer work-up.

The S-phase fraction is the percentage of cells in a sample that are replicating (copying) their DNA. DNA replication means that the cell is getting ready to divide into 2 new cells. The rate of cancer cell division can also be estimated by a Ki-67 test. If the S-phase fraction or Ki-67 labeling index is high, it means that the cancer cells are dividing more rapidly, which indicates a more aggressive cancer.

Tests of gene patterns

Researchers have found that looking at the patterns of a number of different genes at the same time (sometimes referred to as gene expression profiling) can help predict whether or not an early stage breast cancer is likely to come back after initial treatment. Two such tests, which look at different sets of genes, are now available: the Oncotype DX® and the MammaPrint®

Oncotype DX®: The Oncotype DX test may be helpful when deciding whether additional (adjuvant) treatment with chemotherapy (after surgery) might be useful in women with certain early-stage breast cancers that usually have a low chance of coming back (stage I or II estrogen receptor–positive breast cancers without lymph node involvement). Recent data has shown it may also be helpful for patients with positive lymph nodes.

The test looks at a set of 21 genes in cells from tumor samples to determine a 'recurrence score', which is a number between 0 and 100:

- Women with a recurrence score of 17 or below have a low risk of recurrence (coming back after treatment).

- Those with a score of 18 to 30 are at intermediate risk.

- Women with a score of 31 or more are at high risk.

The test estimates risk, but it cannot tell for certain if any particular woman will have a recurrence. It is a tool that can be used, along with other factors, to help guide women and their doctors when deciding whether more treatment might be useful.

MammaPrint®: This test can be used to help determine how likely certain early-stage (stage I or II) breast cancers are to recur in a distant part of the body after initial treatment. It can be used for either ER-negative or ER-positive tumors.

The test looks at the activity of 70 different genes to determine if the cancer is low risk or high risk. This may help doctors decide if further (adjuvant) treatment might be needed.

To do a MammaPrint test, the tumor must be collected and stored in a certain way, so the decision to do this test must be made before surgery.

Usefulness of these tests: While some doctors are using these tests (along with other information) to help make decisions about offering chemotherapy, others are waiting for more research to prove they are helpful. Large clinical trials of these tests are now being done. In the meantime, women may want to discuss with their doctors whether or not these tests might be useful for them.

How is breast cancer staged?

The stage describes the extent of the cancer in the body. It is based on whether the cancer is invasive or non-invasive, the size of the tumor, how many lymph nodes are involved, and if it has spread to other parts of the body. The stage of a cancer is one of the most important factors in determining prognosis and treatment options.

Staging is the process of finding out how widespread a cancer is when it is diagnosed. Depending on the results of your physical exam and biopsy, your doctor may want you to have certain imaging tests such as a chest x-ray, mammograms of both breasts, bone scans, computed tomography (CT) scans, magnetic resonance imaging (MRI), and/or positron emission tomography (PET) scans (see below). Blood tests may also be done to evaluate your overall health and help find out if the cancer has spread to certain organs.

Imaging tests that look for breast cancer spread

Once breast cancer is diagnosed, one or more of the following tests may be done.

Chest x-ray

This test may be done to see whether the breast cancer has spread to your lungs.

Mammogram

If they haven't been done already, more extensive mammograms may be done to get more thorough views of the breasts. This is to check for any other abnormal areas that could be cancer as well. This test is described in the section, "How is breast cancer diagnosed?"

Bone scan

A bone scan can help show whether a cancer has spread (metastasized) to your bones. It can be more useful than standard x-rays because it can show all of the bones of the body at the same time.

For this test, a small amount of low-level radioactive material is injected into a vein (intravenously, or IV). The substance settles in areas of bone changes throughout the entire skeleton over the course of a couple of hours. You then lie on a table for about 30 minutes while a special camera detects the radioactivity and creates a picture of your skeleton.

Areas of bone changes appear as "hot spots" on your skeleton -- that is, they attract the radioactivity. These areas may suggest the presence of metastatic cancer, but arthritis or other bone diseases can also cause the same pattern. To distinguish between these conditions, your cancer care team may use other imaging tests such as simple x-rays or CT or MRI scans to get a better look at the areas that light up, or they may even take biopsy samples of the bone.

Computed tomography (CT) scan

The CT scan is an x-ray test that produces detailed cross-sectional images of your body. Instead of taking one picture, like a regular x-ray, a CT scanner takes many pictures as it rotates around you while you lie on a table. A computer then combines these pictures into images of slices of the part of your body being studied. In women with breast cancer, this test is most often used to look at the chest and/or abdomen to see if the cancer has spread to other organs.

Before any pictures are taken, you may be asked to drink 1 to 2 pints of a liquid called *oral contrast*. This helps outline the intestine so that certain areas are not mistaken for tumors. You may also receive an IV (intravenous) line through which a different kind of contrast dye (IV contrast) is injected. This helps better outline structures in your body.

The injection might cause some flushing (a feeling of warmth, especially in the face). Some people are allergic and get hives. Rarely, more serious reactions like trouble breathing or low blood pressure can occur. Medicine can be given to prevent and treat allergic reactions. Be sure to tell the doctor if you have ever had a reaction to any contrast material used for x-rays.

CT scans take longer than regular x-rays. You need to lie still on a table while they are being done. During the test, the table moves in and out of the scanner, a ring-shaped

machine that completely surrounds the table. You might feel a bit confined by the ring you have to lie in while the pictures are being taken.

CT guided needle biopsy: CT scans can also be used to precisely guide a biopsy needle into a suspected area of cancer spread. For this procedure, you remain on the CT scanning table while a radiologist advances a biopsy needle through the skin and toward the location of the mass. CT scans are repeated until the doctors are sure that the needle is within the mass. A fine needle biopsy sample (tiny fragment of tissue) or a core needle biopsy sample (a thin cylinder of tissue about ½-inch long and less than 1/8-inch in diameter) is then removed and sent to be looked at under a microscope.

Magnetic resonance imaging (MRI) scan

This test is described in the sections, "Can breast cancer be found early?"and "How is breast cancer diagnosed?" as an imaging test of the breast. It may be used to examine the breast with cancer, to look for other tumors. It may also be used to look at the opposite breast, to be sure that it does not contain any tumors. It is not yet clear how helpful this is in planning surgery in someone known to have breast cancer.

MRI scans are also used to look for cancer that has spread to various parts of the body, just like CT scans. MRI scans are particularly helpful in looking at the brain and spinal cord.

MRI scans use radio waves and very strong magnets instead of x-rays. The energy from the radio waves is absorbed and then released in a pattern formed by the type of body tissue and by certain diseases. A computer translates the pattern into a very detailed image of parts of the body. A contrast material called *gadolinium* is often injected into a vein before the scan to better see details.

MRI scans are a little more uncomfortable than CT scans. First, they take longer -- often up to an hour. Second, you have to lie inside a narrow tube, which is confining and can upset people with claustrophobia (a fear of enclosed spaces). Newer, "open" MRI machines can sometimes help with this if needed. The machine also makes buzzing and clicking noises that you may find disturbing. Some centers provide headphones with music to block this noise out.

Ultrasound

This test is described in the section "How is breast cancer diagnosed?"as an imaging test of the breast. But ultrasound can also be used to look for cancer that has spread to some other parts of the body.

Ultrasound tests use sound waves and their echoes to produce a picture of internal organs or masses. A small microphone-like instrument called a *transducer* sends out sound waves and picks up the echoes as they bounce off body tissues. The echoes are converted by a computer into a black and white image that is shown on a computer screen. This test is painless and does not expose you to radiation.

Abdominal ultrasound can be used to look for tumors in your liver or other abdominal organs. When you have an abdominal ultrasound exam, you simply lie on a table and a technician moves the transducer over the skin overlying the part of your body being examined. Usually, the skin is first lubricated with gel.

Positron emission tomography (PET) scan

For a PET scan, glucose (a form of sugar) that contains a radioactive atom is injected into the bloodstream. Because cancer cells in the body are growing rapidly, they absorb large amounts of the radioactive sugar. After about an hour, a special camera is used to create a picture of areas of radioactivity in the body.

A PET scan is useful when your doctor thinks the cancer may have spread but doesn't know where. The picture is not finely detailed like a CT or MRI scan, but it provides helpful information about your whole body. Some newer machines are able to do both a PET and CT scan at the same time (PET/CT scan). This allows the radiologist to compare areas of higher radioactivity on the PET with the appearance of that area on the CT.

So far, most studies show it isn't very helpful in most cases of breast cancer, but it may be used when the cancer is known to have spread.

The American Joint Committee on Cancer (AJCC) TNM system

A staging system is a standardized way for the cancer care team to summarize information about how far a cancer has spread. The most common system used to describe the stages of breast cancer is the American Joint Committee on Cancer (AJCC) TNM system.

The stage of a breast cancer can be based either on the results of physical exam, biopsy, and imaging tests (called the *clinical stage*), or on the results of these tests plus the results of surgery (called the *pathologic stage*). The staging described here is the pathologic stage, which includes the findings after surgery, when the pathologist has looked at the breast mass and nearby lymph nodes. Pathologic staging is likely to be more accurate than clinical staging, as it allows the doctor to get a firsthand impression of the extent of the cancer.

The TNM staging system classifies cancers based on their T, N, and M stages:

- The letter T followed by a number from 0 to 4 describes the tumor's size and spread to the skin or to the chest wall under the breast. Higher T numbers mean a larger tumor and/or wider spread to tissues near the breast.

- The letter N followed by a number from 0 to 3 indicates whether the cancer has spread to lymph nodes near the breast and, if so, how many lymph nodes are affected.

- The letter M followed by a 0 or 1 indicates whether the cancer has spread to distant organs -- for example, the lungs or bones.

Primary tumor (T) categories:

TX: Primary tumor cannot be assessed.

T0: No evidence of primary tumor.

Tis: Carcinoma in situ (DCIS, LCIS, or Paget disease of the nipple with no associated tumor mass)

T1: Tumor is 2 cm (3/4 of an inch) or less across.

T2: Tumor is more than 2 cm but not more than 5 cm (2 inches) across.

T3: Tumor is more than 5 cm across.

T4: Tumor of any size growing into the chest wall or skin. This includes inflammatory breast cancer.

Nearby lymph nodes (N) (based on looking at them under a microscope):

Lymph node staging for breast cancer has changed over time as technology has evolved. Earlier methods were useful in finding large deposits of cancer cells in the lymph nodes, but could miss microscopic areas of cancer spread. Over time, newer methods have made it possible to find smaller and smaller deposits of cancer cells. Experts haven't been sure what to do with the new information. Do tiny deposits of cancer cells affect outlook the same way that larger deposits do? How much cancer in the lymph node is needed to see a change in outlook or treatment?

These questions are still being studied, but for now, a deposit of cancer cells must contain at least 200 cells or be at least 0.2 mm across (less than 1/100 of an inch) for it to change the N stage. An area of cancer spread that is smaller than 0.2 mm (or less than 200 cells) doesn't change the stage, but is recorded with abbreviations that reflect the way the cancer spread was detected. The abbreviation "i+" means that cancer cells were only seen when a special stain, called immunohistochemistry, was used. The abbreviation "mol+" is used if the cancer could only be found using a technique called PCR. These very tiny areas are sometimes called *isolated tumor cells*. If the area of cancer spread is at least 0.2 mm (or 200 cells), but still not larger than 2 mm, it is called a micrometastasis (one mm is about the size of the width of a grain of rice). Micrometastases are counted only if there aren't any larger areas of cancer spread. Areas of cancer spread larger than 2 mm are known to affect outlook and do change the N stage. These larger areas are sometimes called macrometastases, but may just be called metastases.

NX: Nearby lymph nodes cannot be assessed (for example, removed previously).

N0: Cancer has not spread to nearby lymph nodes.

> **N0(i+)**: Tiny amounts of cancer are found in underarm lymph nodes by using special stains. The area of cancer spread contains less than 200 cells and is smaller than 0.2 mm.

N0(mol+): Cancer cells cannot be seen in underarm lymph nodes (even using special stains), but traces of cancer cells were detected using a special test (called PCR).

N1: Cancer has spread to 1 to 3 axillary (underarm) lymph node(s), and/or tiny amounts of cancer are found in internal mammary lymph nodes (those near the breast bone) on sentinel lymph node biopsy.

> **N1mi**: Micrometastases (tiny areas of cancer spread) in 1 to 3 lymph nodes under the arm. The areas of cancer spread in the lymph nodes are 2 mm or less across (but at least 200 cancer cells or 0.2mm across).

> **N1a**: Cancer has spread to 1 to 3 lymph nodes under the arm with at least one area of cancer spread greater than 2 mm across.

> **N1b**: Cancer has spread to internal mammary lymph nodes, but this spread could only be found on sentinel lymph node biopsy (it did not cause the lymph nodes to become enlarged).

> **N1c**: Both N1a and N1b apply.

N2: Cancer has spread to 4 to 9 lymph nodes under the arm, or cancer has enlarged the internal mammary lymph nodes (either N2a or N2b, but not both).

> **N2a**: Cancer has spread to 4 to 9 lymph nodes under the arm, with at least one area of cancer spread larger than 2 mm.

> **N2b**: Cancer has spread to one or more internal mammary lymph nodes, causing them to become enlarged.

N3: Any of the following:

> **N3a**: either
>
> - Cancer has spread to 10 or more axillary lymph nodes, with at least one area of cancer spread greater than 2mm, OR
>
> - Cancer has spread to the lymph nodes under the clavicle (collar bone), with at least one area of cancer spread greater than 2mm.
>
> **N3b**: either:
>
> - Cancer is found in at least one axillary lymph node (with at least one area of cancer spread greater than 2 mm) and has enlarged the internal mammary lymph nodes, OR
>
> - Cancer involves 4 or more axillary lymph nodes (with at least one area of cancer spread greater than 2 mm), and tiny amounts of cancer are found in internal mammary lymph nodes on sentinel lymph node biopsy.
>
> **N3c**: Cancer has spread to the lymph nodes above the clavicle with at least one area of cancer spread greater than 2mm.

Metastasis (M):

MX: Presence of distant spread (metastasis) cannot be assessed.

M0: No distant spread is found on x-rays (or other imaging procedures) or by physical exam.

>**cM0(i +)**: Small numbers of cancer cells are found in blood or bone marrow (found only by special tests), or tiny areas of cancer spread (no larger than 0.2 mm) are found in lymph nodes away from the breast.

M1: Spread to distant organs is present. (The most common sites are bone, lung, brain, and liver.)

Breast cancer stage grouping

Once the T, N, and M categories have been determined, this information is combined in a process called *stage grouping*. Cancers with similar stages tend to have a similar outlook and thus are often treated in a similar way. Stage is expressed in Roman numerals from stage I (the least advanced stage) to stage IV (the most advanced stage). Non-invasive cancer is listed as stage 0.

Stage 0: Tis, N0, M0: This is *ductal carcinoma in situ (DCIS)*, the earliest form of breast cancer. In DCIS, cancer cells are still within a duct and have not invaded deeper into the surrounding fatty breast tissue. *Lobular carcinoma in situ (LCIS)* is sometimes also classified as stage 0 breast cancer, but most oncologists believe it is not a true breast cancer. In LCIS, abnormal cells grow within the lobules or milk-producing glands, but they do not penetrate through the wall of these lobules. Paget disease of the nipple (without an underlying tumor mass) is also stage 0. In all cases the cancer has not spread to lymph nodes or distant sites.

Stage IA: T1, N0, M0: The tumor is 2 cm (about 3/4 of an inch) or less across (T1) and has not spread to lymph nodes (N0) or distant sites (M0).

Stage IB: T0 or T1, N1mi, M0: The tumor is 2 cm or less across (or is not found) (T0 or T1) with micrometastases in 1 to 3 axillary lymph nodes (the cancer in the lymph nodes is greater than 0.2mm across and/or more than 200 cells but is not larger than 2 mm)(N1mi). The cancer has not spread to distant sites (M0).

Stage IIA: One of the following applies:

T0 or T1, N1 (but not N1mi), M0: The tumor is 2 cm or less across (or is not found) (T1 or T0) and either:

- It has spread to 1 to 3 axillary lymph nodes, with the cancer in the lymph nodes larger than 2 mm across (N1a), OR

- Tiny amounts of cancer are found in internal mammary lymph nodes on sentinel lymph node biopsy (N1b), OR

- It has spread to 1 to 3 lymph nodes under the arm and to internal mammary lymph nodes (found on sentinel lymph node biopsy) (N1c).

OR

T2, N0, M0: The tumor is larger than 2 cm across and less than 5 cm (T2) but hasn't spread to the lymph nodes (N0).

The cancer hasn't spread to distant sites (M0).

Stage IIB: One of the following applies:

T2, N1, M0: The tumor is larger than 2 cm and less than 5 cm across (T2). It has spread to 1 to 3 axillary lymph nodes and/or tiny amounts of cancer are found in internal mammary lymph nodes on sentinel lymph node biopsy (N1). The cancer hasn't spread to distant sites (M0).

OR

T3, N0, M0: The tumor is larger than 5 cm across but does not grow into the chest wall or skin and has not spread to lymph nodes (T3, N0). The cancer hasn't spread to distant sites (M0).

Stage IIIA: One of the following applies:

T0 to T2, N2, M0: The tumor is not more than 5 cm across (or cannot be found) (T0 to T2). It has spread to 4 to 9 axillary lymph nodes, or it has enlarged the internal mammary lymph nodes (N2). The cancer hasn't spread to distant sites (M0).

OR

T3, N1 or N2, M0: The tumor is larger than 5 cm across but does not grow into the chest wall or skin (T3). It has spread to 1 to 9 axillary nodes, or to internal mammary nodes (N1 or N2). The cancer hasn't spread to distant sites (M0).

Stage IIIB: T4, N0 to N2, M0: The tumor has grown into the chest wall or skin (T4), and one of the following applies:

- It has not spread to the lymph nodes (N0).

- It has spread to 1 to 3 axillary lymph nodes and/or tiny amounts of cancer are found in internal mammary lymph nodes on sentinel lymph node biopsy (N1).

- It has spread to 4 to 9 axillary lymph nodes, or it has enlarged the internal mammary lymph nodes (N2).

The cancer hasn't spread to distant sites (M0).

Inflammatory breast cancer is classified as T4 and is stage IIIB unless it has spread to distant lymph nodes or organs, in which case it would be stage IV.

Stage IIIC: any T, N3, M0: The tumor is any size (or can't be found), and one of the following applies:

- Cancer has spread to 10 or more axillary lymph nodes (N3).

- Cancer has spread to the lymph nodes under the clavicle (collar bone) (N3).

- Cancer has spread to the lymph nodes above the clavicle (N3).

- Cancer involves axillary lymph nodes and has enlarged the internal mammary lymph nodes (N3).

- Cancer has spread to 4 or more axillary lymph nodes, and tiny amounts of cancer are found in internal mammary lymph nodes on sentinel lymph node biopsy (N3).

The cancer hasn't spread to distant sites (M0).

Stage IV: any T, any N, M1: The cancer can be any size (any T) and may or may not have spread to nearby lymph nodes (any N). It has spread to distant organs or to lymph nodes far from the breast (M1). The most common sites of spread are the bone, liver, brain, or lung,

If you have any questions about the stage of your cancer and what it might mean in your case, be sure to ask your doctor.

Breast cancer survival rates by stage

Survival rates are often used by doctors as a standard way of discussing a person's prognosis (outlook). Some patients with cancer may want to know the survival statistics for people in similar situations, while others may not find the numbers helpful, or may even not want to know them. It's up to you if you want to read about the survival statistics below for breast cancer.

The 5-year survival rate refers to the percentage of patients who live at least 5 years after being diagnosed with cancer. Many of these patients live much longer than 5 years after diagnosis. Also, people diagnosed with cancer can die from other things, and these numbers do not take into account the fact that some of the deaths are from causes other than breast cancer.

In order to get 5-year survival rates, doctors have to look at people who were treated at least 5 years ago. Improvements in treatment since then may result in a more favorable outlook for people now being diagnosed with (cancer).

Survival rates are often based on previous outcomes of large numbers of people who had the disease, but they cannot predict what will happen in any particular person's case. Many other factors may affect a person's outlook, such as the the grade of the cancer and the presence of hormone receptors on the cancer cells. Your doctor can tell you how the numbers below may apply to you, as he or she is familiar with the aspects of your particular situation.

The available statistics do not divide survival rates by all of the substages, such as IA and IB. The rates for these substages are likely to be close to the rate for the overall stage. For

example, the survival rate for stage IA is likely to be slightly higher than that listed for stage I, while the survival rate for stage IB would be expected to be slightly lower.

The numbers below come from the National Cancer Data Base, and are based on people who were diagnosed with breast cancer in 2001 and 2002.

Stage	5-year Survival Rate
0	93%
I	88%
IIA	81%
IIB	74%
IIIA	67%
IIIB	41%*
IIIC	49%*
IV	15%

*These numbers are correct as written (stage IIIB shows worse survival than stage IIIC).

How is breast cancer treated?

This information represents the views of the doctors and nurses serving on the American Cancer Society's Cancer Information Database Editorial Board. These views are based on their interpretation of studies published in medical journals, as well as their own professional experience.

The treatment information in this document is not official policy of the Society and is not intended as medical advice to replace the expertise and judgment of your cancer care team. It is intended to help you and your family make informed decisions, together with your doctor.

Your doctor may have reasons for suggesting a treatment plan different from these general treatment options. Don't hesitate to ask him or her questions about your treatment options.

This section starts with general comments about the types of treatments used for breast cancer. This is followed by a discussion of the typical treatment options based on the stage of the cancer (and a small section on breast cancer treatment during pregnancy).

General types of treatment

Treatents can be classified into broad groups, based on how they work and when they are used.

Local versus systemic therapy

Local therapy is intended to treat a tumor at the site without affecting the rest of the body. Surgery and radiation therapy are examples of local therapies.

Systemic therapy refers to drugs which can be given by mouth or directly into the bloodstream to reach cancer cells anywhere in the body. Chemotherapy, hormone therapy, and targeted therapy are systemic therapies.

Adjuvant and neoadjuvant therapy

Patients who have no detectable cancer after surgery are often given adjuvant (additional) systemic therapy. Doctors believe that in some cases cancer cells may break away from the primary breast tumor and begin to spread through the body by way of the bloodstream even in the early stages of the disease. These cells can't be felt on a physical exam or seen on x-rays or other imaging tests, and they cause no symptoms. But they can go on to become new tumors in other organs or in bones. The goal of adjuvant therapy is to kill these hidden cells.

Not every patient needs adjuvant therapy. Generally speaking, if the tumor is larger or the cancer has spread to lymph nodes, it is more likely to have spread through the bloodstream. But there are other features, some of which have been previously discussed, that may determine if a patient should get adjuvant therapy. Recommendations about adjuvant therapy are discussed in the sections on these treatments and in the section on treatment by stage.

Some patients are given treatment, such as chemotherapy or hormone therapy, before surgery. The goal of this treatment is to shrink the tumor in the hope it will allow a less extensive operation to be done. This is called *neoadjuvant therapy*.

Surgery for breast cancer

Most women with breast cancer have some type of surgery. Surgery is often needed to remove a breast tumor. Options for this include breast-conserving surgery and mastectomy. Breast reconstruction can be done at the same time as the mastectomy or done later on. Surgery is also used to check the lymph nodes under the arm for cancer spread. Options for this include a sentinel lymph node biopsy and an axillary (armpit) lymph node dissection.

Breast-conserving surgery

This type of surgery is sometimes called p*artial (or segmental) mastectomy.* It only removes a part of the affected breast, but how much is removed depends on the size and location of the tumor and other factors. If radiation therapy is to be given after surgery, small metallic clips (which will show up on x-rays) may be placed inside the breast during surgery to mark the area for the radiation treatments.

Lumpectomy removes only the breast lump and a surrounding margin of normal tissue. Radiation therapy is usually given after a lumpectomy. If adjuvant chemotherapy is to be given as well, radiation is usually delayed until the chemotherapy is completed.

Quadrantectomy removes more breast tissue than a lumpectomy. For a quadrantectomy, one-quarter of the breast is removed. Radiation therapy is usually given after surgery. Again, this may be delayed if chemotherapy is to be given as well.

If cancer cells are found at any of the edges of the piece of tissue removed, it is said to have *positive margins*. When no cancer cells are found at the edges of the tissue, it is said to have *negative* or *clear margins*. The presence of positive margins means that that some cancer cells may have been left behind after surgery. If the pathologist finds positive margins in the tissue removed with surgery, the surgeon may need to go back and remove more tissue. This operation is called a *re-excision*. If the surgeon can't remove enough breast tissue to get clear surgical margins, a mastectomy may be needed.

For most women with stage I or II breast cancer, breast-conservation therapy (lumpectomy/partial mastectomy plus radiation therapy) is as effective as mastectomy. Survival rates of women treated with these 2 approaches are the same. But breast-conservation therapy is not an option for all women with breast cancer (see the section, "Choosing between lumpectomy and mastectomy" below).

Radiation therapy can sometimes be omitted as a part of breast-conserving therapy. This is somewhat controversial, so women may consider lumpectomy without radiation therapy if all of the following are true:

- They are age 70 years or older.

- They have a tumor that measures 2 cm or less across that has been completely removed (with clear margins).

- The tumor is hormone receptor-positive, and the women are getting hormone therapy (such as tamoxifen or an aromatase inhibitor).

- No lymph nodes contained cancer.

You should discuss this possibility with your health care team.

Possible side effects: Side effects of these operations can include pain, temporary swelling, tenderness, and hard scar tissue that forms in the surgical site. As with all operations, bleeding and infection at the surgery site are also possible.

The larger the portion of breast removed, the more likely it is that there will be a noticeable change in the shape of the breast afterward. If the breasts look very different after surgery, it may be possible to have some type of reconstructive surgery (see the section, "Reconstructive surgery"), or to have the unaffected breast reduced in size to make the breasts more symmetrical. It may even be possible to have this done during the initial surgery. It's very important to talk with your doctor (and possibly a plastic surgeon) before surgery to get an idea of how your breasts are likely to look afterward, and to learn what your options might be.

Mastectomy

Mastectomy is surgery to remove the entire breast. All of the breast tissue is removed, sometimes along with other nearby tissues.

Simple mastectomy: In this procedure, also called *total mastectomy*, the surgeon removes the entire breast, including the nipple, but does not remove underarm lymph nodes or muscle tissue from beneath the breast. Sometimes this is done for both breasts (a double mastectomy), especially when it is done as preventive surgery in women at very high risk for breast cancer. Most women, if they are hospitalized, can go home the next day.

Skin-sparing mastectomy: For some women considering immediate reconstruction, a skin-sparing mastectomy can be done. In this procedure, most of the skin over the breast (other than the nipple and areola) is left intact. This can work as well as a simple mastectomy. The amount of breast tissue removed is the same as with a simple mastectomy.

This approach is only used when immediate breast reconstruction is planned. It may not be suitable for larger tumors or those that are close to the skin. Implants or tissue from other parts of the body are used to reconstruct the breast. This approach has not been used for as long as the more standard type of mastectomy, but many women prefer it because it offers the advantage of less scar tissue and a reconstructed breast that seems more natural.

A variation of the skin-sparing mastectomy is the *nipple-sparing mastectomy*. This procedure is more often an option for women who have a small early stage cancer near the outer part of the breast, with no signs of cancer in the skin or near the nipple. In this procedure, the breast tissue is removed, but the breast skin and nipple are left in place. This is followed by breast reconstruction. The surgeon often removes the breast tissue beneath the nipple (and areola) during the procedure, to check for cancer cells. If cancer is found in this tissue, the nipple is involved with cancer and must be removed. Even when no cancer is found under the nipple, some doctors give the nipple tissue a dose of radiation during or after the surgery to try and reduce the risk of the cancer coming back.

There are still some problems with nipple-sparing surgeries. Afterward, the nipple does not have a good blood supply, so sometimes it can wither away or become deformed. Because the nerves are also cut, there is little or no feeling left in the nipple. In women with larger breasts, the nipple may look out of place after the breast is reconstructed. As a result, many doctors feel that this surgery is best done in women with small to medium sized breasts. This procedure leaves less visible scars, but if it isn't done properly, it can leave behind more breast tissue than other forms of mastectomy. This could result in a higher risk of cancer developing in than for a skin-sparing or simple mastectomy. This was a problem in the past, but improvements in technique have helped make this surgery safer. Still, many experts consider nipple-sparing procedures too risky to be a standard treatment of breast cancer.

Modified radical mastectomy: This procedure is a simple mastectomy plus removal of axillary (underarm) lymph nodes. Surgery to remove these lymph nodes is discussed in further detail later in this section.

Radical mastectomy: In this extensive operation, the surgeon removes the entire breast, axillary lymph nodes, and the pectoral (chest wall) muscles under the breast. This surgery was once very common, but it was found that a modified radical mastectomy was just as effective. This meant that the disfigurement and side effects of a radical mastectomy were not needed, so these surgeries are rarely done now. This operation may still be done for large tumors that are growing into the pectoral muscles under the breast.

Possible side effects: Aside from post-surgical pain and the obvious change in the shape of the breast(s), possible side effects of mastectomy include wound infection, hematoma (buildup of blood in the wound), and seroma (buildup of clear fluid in the wound). If axillary lymph nodes are also removed, other side effects may occur (see the section, "Axillary lymph node dissection").

Choosing between lumpectomy and mastectomy

Many women with early-stage cancers can choose between breast-conserving surgery and mastectomy.

The main advantage of a lumpectomy is that it allows a woman to keep most of her breast. A disadvantage is the usual need for radiation therapy -- most often for 5 to 6 weeks -- after surgery. A small number of women having breast-conserving surgery may not need radiation while a small percentage of women who have a mastectomy will still need radiation therapy to the breast area.

When deciding between a lumpectomy and mastectomy, be sure to get all the facts. You may have an initial gut preference for mastectomy as a way to "take it all out as quickly as possible." This feeling can lead women tend to prefer mastectomy more often than their surgeons do. But the fact is that in most cases, mastectomy does not give you any better chance of long-term survival or a better outcome from treatment. Studies following thousands of women for more than 20 years show that when a lumpectomy can be done, doing mastectomy instead does not provide any better chance of survival.

Most women and their doctors prefer lumpectomy and radiation therapy when it's a reasonable option, but your choice will depend on a number of factors, such as:

- How you feel about losing your breast

- How you feel about getting radiation therapy

- How far you would have to travel and how much time it would take to have radiation therapy

- Whether you think you will want to have more surgery to reconstruct your breast after having a mastectomy

- Your preference for mastectomy as a way to get rid of all your cancer as quickly as possible

- Your fear of the cancer coming back

For some women, mastectomy may clearly be a better option. For example, lumpectomy or breast conservation therapy is usually not recommended for:

- Women who have already had radiation therapy to the affected breast

- Women with 2 or more areas of cancer in the same breast that are too far apart to be removed through 1 surgical incision, while keeping the appearance of the breast satisfactory

- Women whose initial lumpectomy along with re-excision(s) has not completely removed the cancer

- Women with certain serious connective tissue diseases such as scleroderma or lupus, which may make them especially sensitive to the side effects of radiation therapy

- Pregnant women who would require radiation while still pregnant (risking harm to the fetus)

- Women with large tumors (greater than 5 cm (2 inches) across) that didn't shrink very much with neoadjuvant chemotherapy

- Women with inflammatory breast cancer

- Women with a cancer that is large relative to her breast size

Other factors may need to be taken into account as well. For example, young women with breast cancer and a known BRCA mutation are at very high risk for a second cancer. These women often consider having the other breast removed to reduce this risk, and so may choose to have the cancer treated with a mastectomy, as well. A double mastectomy may be done to both treat the cancer and reduce the risk of a second breast cancer.

Axillary lymph node dissection

To determine if the breast cancer has spread to axillary (underarm) lymph nodes, some of these lymph nodes may be removed and looked at under the microscope. This is an important part of staging and determining treatment and outcomes. When the lymph nodes contain cancer cells, there is a higher chance that cancer cells have also spread through the bloodstream to other parts of the body.

As noted above, axillary lymph node dissection is part of a radical or modified radical mastectomy procedure. It may also be done along with a breast-conserving procedure, like a lumpectomy. Anywhere from about 10 to 40 (though usually less than 20) lymph nodes are removed.

The presence of cancer cells in the lymph nodes under the arm is an important factor in considering adjuvant therapy. Axillary dissection is used as a test to help guide other breast cancer treatment decisions.

Possible side effects: As with other operations, pain, swelling, bleeding, and infection are possible.

The main possible long-term effect of removing axillary lymph nodes is lymphedema (swelling) of the arm. This occurs because any excess fluid in the arms normally travels back into the bloodstream through the lymphatic system. Removing the lymph nodes sometimes blocks the drainage from the arm, causing this fluid to remain and build up.

Up to 30% of women who have underarm lymph nodes removed develop lymphedema. It also occurs in up to 3% of women who have a sentinel lymph node biopsy (see below). It may be more common if radiation is given after surgery. Sometimes the swelling lasts for only a few weeks and then goes away. Other times, the swelling lasts a long time. Ways to help prevent or reduce the effects of lymphedema are discussed in the section, "What happens after treatment for breast cancer?". If your arm is swollen, tight, or painful after lymph node surgery, be sure to tell someone on your cancer care team right away.

You may also have short- or long-term limitations in moving your arm and shoulder after surgery. Your doctor may give you exercises to ensure that you do not have permanent problems with movement (a frozen shoulder). Numbness of the skin of the upper, inner arm is another common side effect because the nerve that controls sensation here travels through the lymph node area.

Sentinel lymph node biopsy

Axillary lymph node dissection (ALND) is a safe operation and has low rates of most side effects, in many cases doctors will first use a sentinel lymph node biopsy (SLNB) procedure to check the lymph nodes cancer. This procedure is a way of learning if cancer has spread to lymph nodes without removing all of them.

In this procedure the surgeon finds and removes the first lymph node(s) to which a tumor drains. This lymph node, known as the sentinel node, is the one most likely to contain cancer cells if they have started to spread. To do this, the surgeon injects a radioactive substance and/or a blue dye into the tumor or the area around it. Lymphatic vessels will carry these substances into the sentinel node(s). The doctor can use a special device to detect the radioactivity in the nodes that the radioactive substance flows into or can look for lymph nodes that have turned blue. These are separate ways to find the sentinel node, but are often done together as a double check. The doctor then cuts the skin over the area and removes the node(s) containing the dye (or radiation). These nodes (often 2 or 3) are then looked at closely by the pathologist. (Because fewer nodes are removed than in an ALND, each one can be looked at more closely for any cancer).

If there is no cancer in the sentinel node(s), it's very unlikely that the cancer has spread to other lymph nodes, so no further lymph node surgery is needed. The patient can avoid the potential side effects of a full ALND (see above).

If the sentinel node(s) has cancer, the surgeon will do a full axillary lymph node dissection to see how many other lymph nodes are involved. The lymph node can sometimes be checked for cancer during surgery. If cancer is found in the sentinel lymph node, the surgeon may go on to remove more lymph nodes or even do a full axillary dissection. If no cancer cells are seen in the lymph node at the time of the surgery, or if the sentinel node is not checked at the time of the surgery, the lymph node(s) will be examined in greater detail over the next several days. If cancer is found in the lymph node, the surgeon may recommend a full axillary lymph node dissection at a later time.

Sentinel lymph node biopsy requires a great deal of skill. It should be done only by a surgical team known to have experience with this technique. If you are thinking about having this type of biopsy, ask your health care team if they do them regularly.

Possible side effects: As with other operations, pain, swelling, bleeding, and infection are possible.

The main possible long-term effect of a sentinel lymph node biopsy is lymphedema of the arm. This occurs less often than with a full ALND, but it can still happen. This is discussed in more detail in the section, "Axillary lymph node dissection" (above).

Reconstructive surgery

After having a mastectomy (or some breast-conserving surgeries), a woman may want to consider having the breast mound rebuilt; this is called *breast reconstruction*. These procedures are not done to treat cancer but to restore the breast's appearance after surgery. If you are going to have breast surgery and are thinking about having reconstruction, it is important to consult with a plastic surgeon who is an expert in breast reconstruction before your surgery.

Decisions about the type of reconstruction and when it will be done depend on each woman's medical situation and personal preferences. You may have a choice between having your breast reconstructed at the same time as the mastectomy (immediate reconstruction) or at a later time (delayed reconstruction). There are several types of reconstructive surgery. Some use saline (salt water) or silicone implants, while others use tissues from other parts of your body (autologous tissue reconstruction).

For a discussion of the different reconstruction options, see our document, *Breast Reconstruction After Mastectomy*. You may also find it helpful to talk with a woman who has had the type of reconstruction you might be considering. Our Reach to Recovery volunteers can help you with this.

What to expect with surgery

For many, the thought of surgery can be frightening. But with a better understanding of what to expect before, during, and after the operation, many fears can be relieved.

Before surgery: The common biopsy procedures let you find out if you have breast cancer within a few days of your biopsy, but the extent of the breast cancer will not be known until after imaging tests and the surgery for local treatment are done.

Usually, you meet with your surgeon a few days before the operation to discuss the procedure. This is a good time to ask specific questions about the surgery and review potential risks. Be sure you understand what the extent of the surgery is likely to be and what you should expect afterward. If you are thinking about breast reconstruction, ask about this as well.

You will be asked to sign a consent form, giving the doctor permission to perform the surgery. Take your time and review the form carefully to be certain that you understand what you are signing. Sometimes, doctors send material for you to review in advance of your appointment, so you will have plenty of time to read it and won't feel rushed. You may also be asked to give consent for researchers to use any tissue or blood that is not needed for diagnostic purposes. Although this may not be of direct use to you, it may be very helpful to women in the future.

You may be asked to donate blood before some operations, such as a mastectomy combined with natural tissue reconstruction, if the doctors think a transfusion might be needed. You might feel more secure knowing that if a transfusion is needed, you will receive your own blood. If you do not receive your own blood, it is important to know that in the United States, blood transfusion from another person is nearly as safe as receiving your own blood. Ask your doctor about your possible need for a blood transfusion.

Your doctor will review your medical records and ask you about any medicines you are taking. This is to be sure that you are not taking anything that might interfere with the surgery. For example, if you are taking aspirin, arthritis medicine, or a blood-thinning drug (like coumadin), you may be asked to stop taking the drug about a week or 2 before the surgery. Be sure you tell your doctor about everything you take, including vitamins and herbal supplements. Usually, you will be told not to eat or drink anything for 8 to 12 hours before the surgery, especially if you are going to have general anesthesia (will be asleep during surgery).

You will also meet with the anesthesiologist or nurse anesthetist, the health professional who will be giving you the anesthesia during your surgery. The type of anesthesia used depends largely on the kind of surgery being done and your medical history.

Surgery: Depending on the likely extent of your surgery, you may be offered the choice of an outpatient procedure (where you go home the same day) or you may be admitted to the hospital.

General anesthesia is usually given whenever the surgery involves a mastectomy or an axillary node dissection, and is most often used during breast-conserving surgery as well. You will have an IV (intravenous) line put in (usually in a vein in your arm), which the medical team will use to give medicines that may be needed during the surgery. Usually you will be hooked up to an electrocardiogram (EKG) machine and have a blood pressure

cuff on your arm, so your heart rhythm and blood pressure can be checked during the surgery.

The length of the operation depends on the type of surgery being done. For example, a mastectomy with axillary lymph node dissection will usually take from 2 to 3 hours. After your surgery, you will be taken to the recovery room, where you will stay until you are awake and your condition and vital signs (blood pressure, pulse, and breathing) are stable.

After surgery: How long you stay in the hospital depends on the type of surgery being done, your overall state of health and whether you have any other medical problems, how well you do during the surgery, and how you feel after the surgery. Decisions about the length of your stay should be made by you and your doctor and not dictated by what your insurance will pay, but it is important to check your insurance coverage before surgery.

In general, women having a mastectomy and/or axillary lymph node dissection stay in the hospital for 1 or 2 nights and then go home. However, some women may be placed in a 23-hour, short-stay observation unit before going home.

Less involved operations such as lumpectomy and sentinel lymph node biopsy are usually done in an outpatient surgery center, and an overnight stay in the hospital is usually not needed.

You may have a dressing (bandage) over the surgery site that may wrap snugly around your chest. You may have one or more drains (plastic or rubber tubes) coming out from the breast or underarm area to remove blood and lymph fluid that collects during the healing process. Your health care team will teach you how to care for the drains, which may include emptying and measuring the fluid and identifying problems the doctor or nurse needs to know about. Most drains stay in place for 1 or 2 weeks. When drainage has decreased to about 30 cc (1 fluid ounce) each day, the drain will usually be removed.

Most doctors will want you to start moving your arm soon after surgery so that it won't get stiff.

Many women who have a lumpectomy or mastectomy are often surprised by how little pain they have in the breast area. But they are less happy with the strange sensations (numbness, pinching/pulling feeling) they may feel in the underarm area.

Ask your health care team how to care for your surgery site and arm. Usually, they will give you and your caregivers written instructions about care after surgery. These instructions should include:

- The care of the surgical wound and dressing

- How to monitor drainage and take care of the drains

- How to recognize signs of infection

- When to call the doctor or nurse

- When to begin using the arm and how to do arm exercises to prevent stiffness

- When to resume wearing a bra

- When to begin using a prosthesis and what type to use (after mastectomy)

- What to eat and not to eat

- Use of medications, including pain medicines and possibly antibiotics

- Any restrictions of activity

- What to expect regarding sensations or numbness in the breast and arm

- What to expect regarding feelings about body image

- When to see your doctor for a follow-up appointment

- Referral to a Reach to Recovery volunteer. Through our Reach to Recovery program, a specially trained volunteer who has had breast cancer can provide information, comfort, and support (see our document, *Reach to Recovery* for more information).

Most patients see their doctor about 7 to 14 days after the surgery. Your doctor should explain the results of your pathology report and talk to you about the need for further treatment. If you will need more treatment, you may be referred to a radiation oncologist and/or a medical oncologist. If you are thinking about breast reconstruction, you may be referred to a plastic surgeon as well.

Post-mastectomy pain syndrome

Post-mastectomy pain syndrome (PMPS) is chronic nerve (neuropathic) pain after lumpectomy or mastectomy. Studies have shown that between 20% and 60% of women develop PMPS after surgery, but it is often not recognized as such. The classic signs of PMPS are chest wall pain and tingling down the arm. Pain may also be felt in the shoulder, scar, arm, or armpit. Other common complaints include numbness, shooting or pricking pain, or unbearable itching.

PMPS is thought to be linked to damage done to the nerves in the armpit and chest during surgery. But the causes are not known. Because major surgeries are less often used to treat breast cancer today, PMPS is becoming less of a problem.

It is important to talk to your doctor about any pain you are having. PMPS can cause you to not use your arm the way you should and over time you could lose the ability to use it normally.

PMPS can be treated. Opioids or narcotics are medicines commonly used to treat pain, but they don't always work well for nerve pain. But there are medicines and treatments that do work for this kind of pain. Talk to your doctor to get the pain control you need.

Radiation therapy

Radiation therapy is treatment with high-energy rays or particles that destroy cancer cells. This treatment may be used to kill any cancer cells that remain in the breast, chest wall, or underarm area after breast-conserving surgery. Radiation may also be needed after mastectomy in patients with either a cancer larger than 5 cm in size, or when cancer is found in the lymph nodes.

Radiation therapy can be given in 2 main ways.

External beam radiation

This is the most common type of radiation therapy for women with breast cancer. The radiation is focused from a machine outside the body on the area affected by the cancer.

The extent of radiation depends on whether a lumpectomy or mastectomy was done and whether or not lymph nodes are involved. If a lumpectomy was done, most often the entire breast gets radiation, and an extra boost of radiation is given to the area in the breast where the cancer was removed to prevent it from coming back in that area. Depending on the size and extent of the cancer, radiation may include the chest wall and underarm area as well. In some cases, the area treated may also include supraclavicular lymph nodes (nodes above the collarbone) and internal mammary lymph nodes (nodes beneath the breast bone in the center of the chest).

When given after surgery, external radiation therapy is usually not started until the tissues have been able to heal, often a month or longer. If chemotherapy is to be given as well, radiation therapy is usually delayed until chemotherapy is complete.

Before your treatments start, the radiation team will take careful measurements to determine the correct angles for aiming the radiation beams and the proper dose of radiation. They will make some ink marks or small tattoos on your skin that they will use later as a guide to focus the radiation on the right area. You may want to talk to your health care team to find out if these marks will be permanent.

Lotions, powders, deodorants, and antiperspirants can interfere with external beam radiation therapy, so your health care team may tell you not to use them until treatments are complete.

External radiation therapy is much like getting an x-ray, but the radiation is more intense. The procedure itself is painless. Each treatment lasts only a few minutes, but the setup time -- getting you into place for treatment -- usually takes longer.

The most common way breast radiation is given is 5 days a week (Monday thru Friday) for about 5 to 6 weeks.

Accelerated breast irradiation: The standard approach of giving external radiation for 5 day a week over many weeks can be inconvenient for many women. Some doctors are now using other schedules, such as giving slightly larger daily doses over only 3 weeks. This approach was studied in a large group of women who had been treated with breast

conserving surgery and who did not have cancer spread to underarm lymph nodes. When compared with giving the radiation over 5 weeks, giving it over only 3 weeks was just as good at keeping the cancer from coming back in the same breast over the first 10 years after treatment. Giving radiation in larger doses using fewer treatments is known as *hypofractionated radiation therapy.* Newer approaches now being studied give radiation over an even shorter period of time. In one approach, larger doses of radiation are given each day, but the course of radiation is shortened to only 5 days. *Intraoperative radiation therapy* (IORT) is another approach that gives a single large dose of radiation in the operating room right after lumpectomy (before the breast incision is closed).

Other forms of accelerated radiation are described below in the section, "Brachytherapy." It is hoped that these newer approaches may prove to be at least equal to the current, standard breast irradiation, but few studies have been done comparing these new methods directly to standard radiation therapy. It is not known if all of the newer methods will still be as good as standard radiation after many years. This is why many doctors still consider them to be experimental at this time. Women who are interested in these approaches may want to ask their doctor about taking part in clinical trials of accelerated breast irradiation now going on.

3D-conformal radiotherapy: In this technique, the radiation is given with special machines so that it is aimed better at the area where the tumor was. This allows more of the healthy breast to be spared. Treatments are given twice a day for 5 days. Because only part of the breast is treated, this is considered to be a form of *accelerated partial breast irradiation.*

Possible side effects of external radiation: The main short-term side effects of external beam radiation therapy are swelling and heaviness in the breast, sunburn-like skin changes in the treated area, and fatigue. Your health care team may advise you to avoid exposing the treated skin to the sun because it may make the skin changes worse. Changes to the breast tissue and skin usually go away in 6 to 12 months.

In some women, the breast becomes smaller and firmer after radiation therapy. Having radiation may also affect a woman's chances to have breast reconstruction. Women who have had breast radiation may have problems breast feeding later on. Radiation to the breast can also sometimes damage some of the nerves to the arm. This is called *brachial plexopathy* and can lead to numbness, pain, and weakness in the shoulder, arm and hand.

Radiation therapy of axillary lymph nodes also can cause lymphedema (see the section, "What will happen after treatment for breast cancer?").

In rare cases, radiation therapy may weaken the ribs, which could lead to a fracture. In the past, parts of the lungs and heart were more likely to get some radiation, which could lead to long-term damage of these organs in some women. Modern radiation therapy equipment allows doctors to better focus the radiation beams, so these problems are rare today.

A very rare complication of radiation to the breast is the development of another cancer called angiosarcoma (see the section, "What is breast cancer?"). These rare cancers can grow and spread quickly.

Brachytherapy

Brachytherapy, also known as *internal radiation*, is another way to deliver radiation therapy. Instead of aiming radiation beams from outside the body, radioactive seeds or pellets are placed directly into the breast tissue next to the cancer. It is often used as a way to add an extra boost of radiation to the tumor site (along with external radiation to the whole breast), although it may also be used by itself (see below). Tumor size, location, and other factors may limit who can get brachytherapy.

There are different types of brachytherapy.

Intracavitary brachytherapy: This method of brachytherapy consists of a small balloon attached to a thin tube. The deflated balloon is inserted into the space left by the lumpectomy and is filled with a salt water solution. (This can be done at the time of lumpectomy or within several weeks afterward.) The balloon and tube are left in place throughout treatment (with the end of the tube sticking out of the breast). Twice a day a source of radioactivity is placed into the middle of the balloon through the tube and then removed. This is done for 5 days as an outpatient treatment. The balloon is then deflated and removed. This system goes by the brand name, Mammosite®. This type of brachytherapy can also be considered a form of accelerated partial breast irradiation. Like many forms of accelerated breast irradiation, there are no studies comparing outcomes with this type of radiation directly with standard external beam radiation. It is not known if the long-term outcomes will be as good.

Interstitial brachytherapy: In this approach, several small, hollow tubes called catheters are inserted into the breast around the area of the lumpectomy and are left in place for several days. Radioactive pellets are inserted into the catheters for short periods of time each day and then removed. This method of brachytherapy has been around longer (and has more evidence to support it), but it is not used as much anymore.

While these methods are sometimes used as ways to add a boost of radiation to the tumor site (along with external radiation to the whole breast), they are also being studied in clinical trials as the only source of radiation for women who have had a lumpectomy. In this sense they can also be considered forms of *accelerated partial breast irradiation*. Early results have been promising, but long-term results are not yet available, and it's not yet clear if irradiating only the area around the cancer will reduce the chances of the cancer coming back as much as giving radiation to the whole breast. The results of studies now being done will probably be needed before more doctors recommend accelerated partial breast irradiation as a standard treatment option.

Chemotherapy

Chemotherapy (often called "chemo") is treatment with cancer-killing drugs that may be given intravenously (injected into a vein) or by mouth. The drugs travel through the bloodstream to reach cancer cells in most parts of the body. Chemo is given in cycles, with each period of treatment followed by a recovery period. Treatment usually lasts for several months.

When is chemotherapy used?

There are several situations in which chemotherapy may be recommended.

Adjuvant chemotherapy: When therapy is given to patients with no evidence of cancer after surgery, it is called adjuvant therapy. Surgery is used to remove all of the cancer that can be seen, but adjuvant therapy is used to kill any cancer cells that may have been left behind that can't be seen. Adjuvant therapy after breast-conserving surgery or mastectomy reduces the risk of breast cancer coming back. Both chemotherapy and hormone therapy can be used as adjuvant treatments.

Even in the early stages of the disease, cancer cells may break away from the primary breast tumor and spread through the bloodstream. These cells don't cause symptoms, they don't show up on imaging tests, and they can't be felt during a physical exam. But if they are allowed to grow, they can establish new tumors in other places in the body. The goal of adjuvant chemotherapy is to kill undetected cells that have traveled from the breast.

Neoadjuvant chemotherapy: Chemotherapy given before surgery is called neoadjuvant therapy. Often, neoadjuvant therapy uses the same chemo that is used as adjuvant therapy (only it is given before surgery instead of after). In terms of survival, there is no difference between giving chemo before or after surgery. The major benefit of neoadjuvant chemotherapy is that it can shrink large cancers so that they are small enough to be removed by lumpectomy instead of mastectomy. Another possible advantage of neoadjuvant chemotherapy is that doctors can see how the cancer responds to chemotherapy. If the tumor does not shrink, your doctor may try different chemotherapy drugs.

Chemotherapy for advanced breast cancer: Chemotherapy can also be used as the main treatment for women whose cancer has already spread outside the breast and underarm area at the time it is diagnosed, or if it spreads after initial treatments. The length of treatment depends on whether the cancer shrinks, how much it shrinks, and how a woman tolerates treatment.

How is chemotherapy given?

In most cases (especially for adjuvant and neoadjuvant treatment), chemotherapy is most effective when combinations of more than one drug are used. Many combinations are being used, and it's not clear that any single combination is clearly the best. Clinical studies continue to compare today's most effective treatments against something that may be better.

Some of the most commonly used drug combinations are:

- CMF: cyclophosphamide (Cytoxan®), methotrexate, and 5-fluorouracil (fluorouracil, 5-FU)

- CAF (or FAC): cyclophosphamide, doxorubicin (Adriamycin®), and 5-fluorouracil

- AC: doxorubicin (Adriamycin) and cyclophosphamide

- EC: epirubicin (Ellence®) and cyclophosphamide

- TAC: docetaxel (Taxotere®), doxorubicin (Adriamycin), and cyclophosphamide

- AC → T: doxorubicin (Adriamycin) and cyclophosphamide followed by paclitaxel (Taxol®) or docetaxel (Taxotere) [Trastuzumab (Herceptin®) may be given with the paclitaxel or docetaxel for HER2/neu positive tumors.]

- A → CMF: doxorubicin (Adriamycin), followed by CMF

- CEF (FEC): cyclophosphamide, epirubicin, and 5-fluorouracil (this may be followed by docetaxel)

- TC: docetaxel (Taxotere) and cyclophosphamide

- TCH: docetaxel, carboplatin, and trastuzumab for HER2/neu positive tumors

Other chemotherapy drugs used for treating women with breast cancer include cisplatin, vinorelbine (Navelbine®), capecitabine (Xeloda®), liposomal doxorubicin (Doxil®), gemcitibine (Gemzar®), mitoxantrone, ixabepilone (Ixempra®), and albumin-bound paclitaxel (Abraxane®). The targeted therapy drugs trastuzumab and lapatinib (Tykerb®) may be used with these chemo drugs for tumors that are HER2/neu-positive (these drugs are discussed in more detail in the "Targeted therapy" section).

Doctors give chemotherapy in cycles, with each period of treatment followed by a rest period. The chemotherapy begins on the first day of each cycle, and then the body is given time to recover from the effects of chemotherapy. The chemotherapy drugs are then repeated to start the next cycle. The time between giving the chemotherapy drugs is generally 2 or 3 weeks and varies according the specific chemotherapy drug or combination of drugs. Some drugs are given more often. These cycles generally last for a total time of 3 to 6 months when given as adjuvant therapy, depending on the drugs used. Treatment may be longer for advanced breast cancer.

Dose-dense chemotherapy: Doctors have found that giving the cycles of chemo closer together can lower the chance that the cancer will come back and improve survival in some women. This usually means giving the same chemo that is normally given every 3 weeks (such as AC → T), but giving it every 2 weeks. In addition, a drug (growth factor) to help boost the white blood cell count is given after the chemo to make sure the white blood cell count returns to normal in time for the next cycle. This approach can lead to more side effects and be harder to take, so it is only used for treatment in women with a higher chance of the cancer coming back after treatment.

Possible side effects

Chemotherapy drugs work by attacking cells that are dividing quickly, which is why they work against cancer cells. But other cells in the body, like those in the bone marrow, the lining of the mouth and intestines, and the hair follicles, also divide quickly. These cells are also likely to be affected by chemotherapy, which can lead to side effects. Some women have many side effects while other women may have few.

The side effects of chemotherapy depend on the type of drugs, the amount taken, and the length of treatment. Some of the most common possible side effects include:

- Hair loss

- Mouth sores

- Loss of appetite

- Nausea and vomiting

- Increased chance of infections (due to low white blood cell counts)

- Easy bruising or bleeding (due to low blood platelet counts)

- Fatigue (due to low red blood cell counts and other reasons)

These side effects are usually short-term and go away after treatment is finished. It's important to let your health care team know if you have any side effects, as there are often ways to lessen them. For example, drugs can be given to help prevent or reduce nausea and vomiting.

Several other side effects are also possible. Some of these are only seen with certain chemotherapy drugs. Your cancer care team will give you information about the possible side effects of the specific drugs you are getting.

Menstrual changes: For younger women, changes in menstrual periods are a common side effect of chemotherapy. Premature menopause (not having any more menstrual periods) and infertility (not being able to become pregnant) may occur and may be permanent. Some chemotherapy drugs are more likely to do this than others. The older a woman is when she receives chemotherapy, the more likely it is that she will become infertile or menopausal as a result. When this happens, it can also lead to rapid bone loss from osteoporosis. There are medicines that can treat or help prevent problems with bone loss.

You cannot depend on chemotherapy to prevent pregnancy, and getting pregnant while receiving chemotherapy could lead to birth defects and interfere with treatment. This is why it's important that pre-menopausal women who are sexually active discuss using birth control with their doctor. It is safe to have children after chemotherapy, but it's not safe to get pregnant while on treatment. If you are pregnant when you get breast cancer, you still can be treated. Chemotherapy can be safely given during the last 2 trimesters of pregnancy.

Neuropathy: Several drugs used to treat breast cancer, including the taxanes (docetaxel and paclitaxel), platinum agents (carboplatin, cisplatin), and ixabepilone, can damage nerves outside of the brain and spinal cord. This can sometimes lead to symptoms (mainly in the hands and feet) like numbness, pain, burning or tingling sensations, sensitivity to cold or heat, or weakness. In most cases this goes away once treatment is stopped, but it may be long-lasting in some women.

Heart damage: Doxorubicin, epirubicin, and some other drugs may cause permanent heart damage if used for a long time or in high doses, so doctors often check the patient's heart function before starting one of these drugs. They also carefully control the doses and use echocardiograms or other heart tests to monitor heart function. If the heart function begins to decline, treatment with these drugs will be stopped. Still, in some patients, heart damage takes a long time to develop. They may not show signs of poor heart function until months or years after treatment stops. Heart damage from these drugs happens more often if the targeted therapy drug trastuzumab is used as well, so doctors are more cautious when these drugs are used together.

Hand-foot syndrome: Certain chemo drugs, such as capecitabine and liposomal doxorubicin, can cause problems with irritation that affects the palms of the hands and the soles of the feet. This is called hand-foot syndrome. Early symptoms include numbness, tingling, and redness. If it gets worse, the hands and feet become swollen with discomfort or even pain. The skin may blister, leading to peeling of the skin. There is no specific treatment, but these symptoms gradually get better when the drug is stopped. The best way to prevent severe hand-foot syndrome is to tell your doctor when early symptoms come up, so that the drug dose can be changed. This syndrome can also occur when the drug 5-FU is given as an IV infusion over several days (which is not common in the treatment of breast cancer).

Chemo brain: Another possible side effect of chemotherapy is "chemo brain." Many women who get chemotherapy for breast cancer report a slight decrease in mental functioning. There may be some problems with concentration and memory, which may last a long time. Still, most women do function well after chemotherapy. In studies that have found chemo brain to be a side effect of treatment, the symptoms most often go away within a few years. For more information, see our document, *Chemo brain*.

Increased risk of leukemia: Very rarely, certain chemotherapy drugs can permanently damage the bone marrow, leading to acute myeloid leukemia, a life-threatening cancer of white blood cells. When this happens it is usually within 10 years after treatment. In most women, chemotherapy's benefits in preventing breast cancer from coming back or in extending life are likely to far exceed the risk of this serious but rare complication.

Feeling unwell or tired: Many women do not feel as healthy after receiving chemotherapy as they did before. There is often a residual feeling of body pain or achiness and a mild loss of physical functioning. These are very subtle changes that are only revealed by closely questioning women who have undergone chemotherapy.

Fatigue is another common (but often overlooked) problem for women who have received chemotherapy. This may last up to several years. It can often be helped, so it is important to let your doctor or nurse know about it. For more information on what you can do about fatigue, see our document, *Fatigue in People with Cancer*. Exercise, naps, and conserving energy may be recommended. If there are sleep problems, these can be treated. Sometimes there is depression, which may be helped by counseling and/or medicines.

Hormone therapy

Hormone therapy is another form of systemic therapy. It is most often used as an adjuvant therapy to help reduce the risk of cancer recurrence after surgery, but it can be used as neoadjuvant treatment, as well. It is also used to treat cancer that has come back after treatment or has spread.

A woman's ovaries are the main source of the hormone *estrogen* up until menopause. After menopause, smaller amounts are still made in the body's fat tissue, where a hormone made by the adrenal gland is converted into estrogen.

Estrogen promotes the growth of about 2 out of 3 of breast cancers -- those containing receptors for the hormones estrogen (ER-positive cancers) and/or progesterone (PR-positive cancers). Because of this, several approaches to blocking the effect of estrogen or lowering estrogen levels are used to treat hormone receptor-positive breast cancers. Hormone therapy does not help patients whose tumors are both ER- and PR-negative.

Tamoxifen and toremifene (Fareston®): These anti-estrogen drugs work by temporarily blocking estrogen receptors on breast cancer cells, preventing estrogen from binding to them. They are taken daily as a pill.

For women with hormone receptor-positive cancers, taking tamoxifen after surgery for 5 years reduces the chances of the cancer coming back by about half. Tamoxifen can also be used to treat metastatic breast cancer, as well as to reduce the risk of developing breast cancer in women at high risk. Toremifene works like tamoxifen, but is not used as often.

The most common side effects of these drugs include fatigue, hot flashes, vaginal dryness or discharge, and mood swings.

Some patients whose cancer has spread to their bones may experience a "tumor flare" with pain and swelling in the muscles and bones. This usually subsides quickly, but in some cases the patient may also develop a high calcium level in the blood that cannot be controlled. If this occurs, the treatment may need to be stopped.

Rare, but more serious side effects are also possible. These drugs can increase the risk of developing cancers of the uterus (endometrial cancer and uterine sarcoma). Tell your doctor right away about any unusual vaginal bleeding (a common symptom of both of these cancers). Most uterine bleeding is not from cancer, but this symptom always needs prompt attention.

Another possible serious side effect is blood clots, which usually form in the legs. In some cases, these may lead to a heart attack, stroke, or blockage in the lungs (pulmonary embolism). Call your doctor or nurse right away if you develop pain, redness, or swelling in your lower leg (calf), shortness of breath, chest pain, sudden severe headache, confusion, or trouble speaking or moving.

Depending on a woman's menopausal status, tamoxifen can have different effects on the bones. In pre-menopausal women tamoxifen can cause some bone thinning, but in post-menopausal women it is often good for bone strength. The effects of toremifene on the bones are less clear.

For most women with breast cancer, the benefits of taking these drugs outweigh the risks.

Fulvestrant (Faslodex®): Fulvestrant is a drug that also acts on the estrogen receptor, but instead of blocking it, this drug eliminates it. It is often effective even if the breast cancer is no longer responding to tamoxifen. It is given by injection once a month. Hot flashes, mild nausea, and fatigue are the major side effects. It is currently only approved for use in post-menopausal women with advanced breast cancer that no longer responds to tamoxifen or toremifene.

Aromatase inhibitors (AIs): Three drugs that stop estrogen production in post-menopausal women have been approved to treat both early and advanced breast cancer: letrozole (Femara®), anastrozole (Arimidex®), and exemestane (Aromasin®). They work by blocking an enzyme (aromatase) responsible for making small amounts of estrogen in post-menopausal women. They cannot stop the ovaries of pre-menopausal women from making estrogen, so they are only effective in post-menopausal women. These drugs are taken daily as pills.

Several studies have compared these drugs with tamoxifen as adjuvant hormone therapy in post-menopausal women. Using these drugs, either alone or after tamoxifen, has been shown to better reduce the risk of cancer recurrence than using tamoxifen alone for 5 years. Schedules that are known to be helpful include:

- Tamoxifen for 2 to 3 years, followed by an aromatase inhibitor (AI) to complete 5 years of treatment

- Tamoxifen for 5 years, followed by an AI for 5 years

- An AI for 5 years

For post-menopausal women whose cancers are hormone receptor–positive, most doctors now recommend using an AI at some point during adjuvant therapy. But it's not yet clear if starting adjuvant therapy with one of these drugs is better than giving tamoxifen and then switching to an AI. We still don't know if giving these drugs for more than 5 years is more helpful than stopping at 5 years. It is also not known if any one of these drugs is better than the others. Studies now being done should help answer these questions.

The AIs tend to have fewer serious side effects than tamoxifen -- they don't cause uterine cancers and very rarely cause blood clots. They can, however, cause muscle pain and joint stiffness and/or pain. The joint pain may be similar to a new feeling of having arthritis in many different joints at one time. This side effect may improve by switching to a different AI, but it has led some women to stop drug treatment. If this occurs, most doctors recommend using tamoxifen to complete 5 years of hormone treatment.

Because aromatase inhibitors remove all estrogens from women after menopause, they also cause bone thinning, sometimes leading to osteoporosis and even fractures. Many women treated with an aromatase inhibitor are also treated with medicine to strengthen their bones, such as bisphosphonates.

Ovarian ablation: In pre-menopausal women, removing or shutting down the ovaries, which are the main source of estrogens, effectively makes the woman post-menopausal. This may allow some other hormone therapies to work better.

Permanent ovarian ablation can be done by surgically removing the ovaries. This operation is called an oophorectomy. More often, ovarian ablation is done with drugs called luteinizing hormone-releasing hormone (LHRH) analogs, such as goserelin (Zoladex®) or leuprolide (Lupron®). These drugs stop the signal that the body sends to ovaries to make estrogens. They can be used alone or with tamoxifen as hormone therapy in pre-menopausal women. They are also being studied as adjuvant therapies along with aromatase inhibitors in pre-menopausal women.

Chemotherapy drugs may also damage the ovaries of pre-menopausal women so they no longer produce estrogen. In some women ovarian function returns months or years later, but in others, the damage to the ovaries is permanent and leads to menopause. This can sometimes be a helpful (if unintended) consequence of chemotherapy with regard to breast cancer treatment, although it leaves the woman infertile.

All of these methods can cause a woman to have symptoms of menopause, including hot flashes, night sweats, vaginal dryness, and mood swings.

Megestrol acetate: Megestrol acetate (Megace®) is a progesterone-like drug used as a hormone treatment of advanced breast cancer, usually for women whose cancers do not respond to the other hormone treatments. Its major side effect is weight gain, and it is sometimes used in higher doses to reverse weight loss in patients with advanced cancer. This is an older drug that is no longer used very often.

Other ways to control hormones: Androgens (male hormones) may be considered after other hormone treatments for advanced breast cancer have been tried. They are sometimes effective, but they can cause masculine characteristics such as an increase in body hair and a deeper voice to develop.

Targeted therapy

As researchers have learned more about the gene changes in cells that cause cancer, they have been able to develop newer drugs that specifically target these changes. These targeted drugs work differently from standard chemotherapy drugs. They often have different (and less severe) side effects. They are most often used along with chemotherapy at this time.

Drugs that target the HER2/neu protein

Trastuzumab (Herceptin): Trastuzumab is a type of drug known as a monoclonal antibody -- a man-made version of a very specific immune system protein. It attaches to a growth-promoting protein known as HER2/neu (or just HER2), which is present in larger than normal amounts on the surface of the breast cancer cells in about 1 of 5 patients. Breast cancers with too much of this protein tend to grow and spread more aggressively.

Trastuzumab can help slow this growth and may also stimulate the immune system to more effectively attack the cancer.

Trastuzumab is given as an injection into a vein (IV), usually once a week or as a larger dose every 3 weeks. The optimal length of time to give it is not yet known.

Trastuzumab is often used (along with chemotherapy) as adjuvant therapy for HER2-positive cancers to reduce the risk of recurrence when the tumor is larger than 1 cm across or when the cancer has spread to the lymph nodes. It is given along with chemotherapy for 3 to 6 months, and then given on its own, usually for a total of a year of treatment. There are ongoing studies looking at how long this drug needs to be given.

Trastuzumab can also shrink some HER2-positive advanced breast cancers that return after chemotherapy or continue to grow during chemotherapy. Treatment that combines trastuzumab with chemotherapy may work better than chemotherapy alone in some patients.

Compared with chemotherapy drugs, the side effects of trastuzumab are relatively mild. They may include fever and chills, weakness, nausea, vomiting, cough, diarrhea, and headache. These side effects occur less often after the first dose.

A more serious potential side effect is heart damage leading to a problem called congestive heart failure. For most (but not all) women, this effect has been temporary and has improved when the drug is stopped. The risk of heart problems is higher when trastuzumab is given with certain chemotherapy drugs such as doxorubicin (Adriamycin) and epirubicin (Ellence). Major symptoms of congestive heart failure are shortness of breath, leg swelling, and severe fatigue. Women having these symptoms should call their doctor right away.

Lapatinib (Tykerb): Lapatinib is another drug that targets the HER2 protein. This drug is given as a pill to women with advanced HER2-positive breast cancer that is no longer helped by chemotherapy and trastuzumab. It is also being studied as an adjuvant therapy in HER2-positive patients, but at this time is only used for advanced breast cancer. In advanced breast cancer, giving lapatinib along with trastuzumab helped patients live longer than giving it alone. The chemotherapy drug capecitabine (Xeloda) is often given as well.

The most common side effects of this drug include diarrhea, nausea, vomiting, rash, and hand-foot syndrome. Diarrhea is a common side effect and can be severe, so it is very important to let your health care team know about any changes in bowel habits as soon as they happen.

In rare cases lapatinib may cause liver problems or a decrease in heart function (that can lead to shortness of breath), although this seems to go away once treatment is finished.

Drugs that target new tumor blood vessels (angiogenesis)

Tumors need to develop and maintain new blood vessels in order to grow. Drugs that target these blood vessels are proving to be helpful against a variety of cancers, including breast cancer.

Bevacizumab (Avastin®) is a monoclonal antibody that has been used in patients with metastatic breast cancer. This antibody is directed against vascular endothelial growth factor, a protein that helps tumors form new blood vessels.

Bevacizumab is given by intravenous (IV) infusion. It is most often used in combination with the chemotherapy drug paclitaxel (Taxol).

Rare, but possibly serious side effects include bleeding, holes forming in the colon (requiring surgery to correct), and slow wound healing.

More common side effects include high blood pressure, tiredness, blood clots, low white blood cell counts, headaches, mouth sores, loss of appetite, and diarrhea. High blood pressure is very common, so it very important that your doctor watches your blood pressure carefully during treatment.

Bevacizumab was first approved by the Food and Drug Administration (FDA) as part of the treatment for metastatic breast cancer in 2008. The approval was based on a study in which the women that received bevacizumab with chemo had a longer time without their cancers growing than the women who received chemo alone. New study results that were presented at a July 2010 FDA meeting did not show a real benefit for the women receiving bevacizumab as a part of their treatment. At this time, the role of this drug in treating breast cancer is not clear.

Bisphosphonates

Bisphosphonates are drugs that are used to help strengthen and reduce the risk of fractures in bones that have been weakened by metastatic breast cancer. Examples include pamidronate (Aredia®) and zoledronic acid (Zometa®). They are given intravenously (IV).

Bisphosphonates may also help against bone thinning (osteoporosis) that can result from treatment with aromatase inhibitors (see above) or from early menopause as a side effect of chemotherapy. There are a number of medicines, including some oral forms of bisphosphonates, to treat loss of bone strength when it is not caused by cancer spread to the bones.

Bisphosphonates can have side effects, including flu-like symptoms and bone pain. A rare but very distressing side effect of intravenous bisphosphonates is damage (osteonecrosis) in the jaw bones (ONJ). It can be triggered by having a tooth extraction (removal) while getting treated with the bisphosphonate. ONJ often appears as an open sore in the jaw that won't heal. It can lead to loss of teeth or infections of the jaw bone. Doctors don't know why this happens or how to treat it, other than to stop the bisphosphonates. Maintaining good oral hygiene by flossing, brushing, making sure that

dentures fit properly, and having regular dental checkups may help prevent this. Most doctors recommend that patients have a dental checkup and have any tooth or jaw problems treated before they start taking a bisphosphonate.

High-dose chemotherapy with stem cell transplant

It is possible to use very high doses of chemotherapy or radiation to kill cancer cells, but such treatments also kill the blood-making stem cells in the bone marrow. Damage to these cells lowers a person's blood cell count. Too few white blood cells can lead to severe infections that could be fatal. Too few platelets make people bleed easily. This, too, can be fatal.

One way to get around this is to remove some of the patient's stem cells from either the peripheral (circulating) blood or bone marrow, give the high-dose treatment, and then return the stem cells into the body through a blood transfusion. The stem cells are able to find their way back into the bone marrow, where they soon re-establish themselves and restore the body's ability to make new blood cells.

At one time it was thought that this would be a good way to treat women with advanced breast cancer. However, several studies have found that women who receive high-dose chemotherapy do not live any longer than women who receive standard chemotherapy without a stem cell transplant. High-dose chemotherapy with stem cell transplant also causes more serious side effects than standard dose chemotherapy.

Research is still being done in this area. New studies may show a benefit, it is likely to be small, and the toxicity from this treatment is very high. At this time, most experts recommend that women with breast cancer not receive high-dose chemotherapy, except as part of a clinical trial.

Clinical trials

You may have had to make a lot of decisions since you've been told you have cancer. One of the most important decisions you will make is choosing which treatment is best for you. You may have heard about clinical trials being done for your type of cancer. Or maybe someone on your health care team has mentioned a clinical trial to you.

Clinical trials are carefully controlled research studies that are done with patients who volunteer for them. They are done to get a closer look at promising new treatments or procedures.

If you would like to take part in a clinical trial, you should start by asking your doctor if your clinic or hospital conducts clinical trials. You can also call our clinical trials matching service for a list of clinical trials that meet your medical needs. You can reach this service at 1-800-303-5691 or on our Web site at http://clinicaltrials.cancer.org. You can also get a list of current clinical trials by calling the National Cancer Institute's Cancer Information Service toll-free at 1-800-4-CANCER (1-800-422-6237) or by visiting the NCI clinical trials Web site at http://www.cancer.gov/clinicaltrials.

There are requirements you must meet to take part in any clinical trial. If you do qualify for a clinical trial, you decide whether or not to enter (enroll in) it.

Clinical trials are one way to get state-of-the art cancer treatment. They are the only way for doctors to learn better methods to treat cancer. Still, they are not right for everyone.

You can get a lot more information on clinical trials in our document called *Clinical Trials: What You Need to Know*. You can read it on our Web site or call our toll-free number (1-800-227-2345) and have it sent to you.

Complementary and alternative therapies

When you have cancer you are likely to hear about ways to treat your cancer or relieve symptoms that your doctor hasn't mentioned. Everyone from friends and family to Internet groups and Web sites offer ideas for what might help you. These methods can include vitamins, herbs, and special diets, or other methods such as acupuncture or massage, to name a few.

What exactly are complementary and alternative therapies?

Not everyone uses these terms the same way, and they are used to refer to many different methods, so it can be confusing. We use *complementary* to refer to treatments that are used *along with* your regular medical care. *Alternative* treatments are used *instead of* a doctor's medical treatment.

Complementary methods: Most complementary treatment methods are not offered as cures for cancer. Mainly, they are used to help you feel better. Some methods that are used along with regular treatment are meditation to reduce stress, acupuncture to help relieve pain, or peppermint tea to relieve nausea. Some complementary methods are known to help, while others have not been tested. Some have been proven not be helpful, and a few have even been found harmful.

Alternative treatments: Alternative treatments may be offered as cancer cures. These treatments have not been proven safe and effective in clinical trials. Some of these methods may pose danger, or have life-threatening side effects. But the biggest danger in most cases is that you may lose the chance to be helped by standard medical treatment. Delays or interruptions in your medical treatments may give the cancer more time to grow and make it less likely that treatment will help.

Finding out more

It is easy to see why people with cancer think about alternative methods. You want to do all you can to fight the cancer, and the idea of a treatment with no side effects sounds great. Sometimes medical treatments like chemotherapy can be hard to take, or they may no longer be working. But the truth is that most of these alternative methods have not been tested and proven to work in treating cancer.

As you consider your options, here are 3 important steps you can take:

- Look for "red flags" that suggest fraud. Does the method promise to cure all or most cancers? Are you told not to have regular medical treatments? Is the treatment a "secret" that requires you to visit certain providers or travel to another country?

- Talk to your doctor or nurse about any method you are thinking about using.

- Contact us at 1-800-227-2345 to learn more about complementary and alternative methods in general and to find out about the specific methods you are looking at.

The choice is yours

Decisions about how to treat or manage your cancer are always yours to make. If you want to use a non-standard treatment, learn all you can about the method and talk to your doctor about it. With good information and the support of your health care team, you may be able to safely use the methods that can help you while avoiding those that could be harmful.

Treatment of stage 0 (non-invasive) breast cancer

The 2 types of non-invasive breast cancers, lobular carcinoma in situ (LCIS) and ductal carcinoma in situ (DCIS), are treated very differently.

LCIS: Since this is not a true cancer, no immediate or active treatment is recommended for most women with LCIS. But because having LCIS increases your risk of developing invasive cancer later on, close follow-up is very important. This usually includes a yearly mammogram and a clinical breast exam. Close follow-up of both breasts is important because women with LCIS in one breast have the same increased risk of developing cancer in either breast. Although there is not enough evidence to recommend routine use of magnetic resonance imaging (MRI) in addition to mammograms for women with LCIS, it is reasonable for these women to talk with their doctors about the benefits and limits of being screened yearly with MRI..

Women with LCIS may also want to consider taking tamoxifen or raloxifene to reduce their risk of breast cancer or taking part in a clinical trial for breast cancer prevention. For more information on drugs to reduce breast cancer risk see our document, *Medicines to Reduce Breast Cancer Risk*. They may also wish to discuss other possible prevention strategies (such as reaching an optimal body weight or starting an exercise program) with their doctor.

Some women with LCIS choose to have a bilateral simple mastectomy (removal of both breasts but not axillary lymph nodes) to reduce their risk of breast cancer, especially if they have other risk factors, such as a strong family history. Depending on the woman's preference, she may consider immediate or delayed breast reconstruction.

DCIS: In most cases, a woman with DCIS can choose between breast-conserving therapy (lumpectomy, usually followed by radiation therapy) and simple mastectomy. Lymph node removal (axillary dissection) is usually not needed. Lumpectomy without radiation therapy is only an option for certain women who had small areas of low-grade DCIS that

was removed with large enough cancer-free surgical margins. But most women who have a lumpectomy, will require radiation therapy.

Mastectomy may be necessary if the area of DCIS is very large, if the breast has several areas of DCIS, or if lumpectomy cannot completely remove the DCIS (that is, the lumpectomy specimen and re-excision specimens have cancer cells in the surgical margins). Women having a mastectomy for DCIS may have reconstruction immediately or later.

If the DCIS is estrogen receptor-positive, treatment with tamoxifen for 5 years after surgery can lower the risk of another DCIS or invasive cancer developing in either breast. Women may want to discuss the pros and cons of this option with their doctors.

Treatment of invasive breast cancer, by stage

Breast-conserving surgery is often appropriate for earlier-stage invasive breast cancers if the cancer is small enough, although mastectomy is also an option. If the cancer is too large, a mastectomy will be needed, unless pre-operative (neoadjuvant) chemotherapy can shrink the tumor enough to allow breast-conserving surgery. In either case, the lymph nodes will need to be checked and removed if they contain cancer. Radiation will be needed for almost all patients who have breast-conserving surgery and some who have mastectomy. Adjuvant systemic therapy after surgery is typically recommended for all cancers larger than 1 cm (about 1/2 inch) across and for some that are smaller.

Stage I

These cancers are still relatively small and have not spread to the lymph nodes or elsewhere.

Local therapy: Stage I cancers can be treated with either breast-conserving surgery (lumpectomy, partial mastectomy) or modified radical mastectomy. The lymph nodes will also need to be evaluated, with a sentinel lymph node biopsy or an axillary lymph node dissection. Breast reconstruction can be done either at the same time as surgery or later.

Radiation therapy is usually given after breast-conserving surgery. Women may consider breast-conserving surgery *without* radiation therapy if all of the following are true:

- They are age 70 years or older.

- The tumor was 2 cm or less across and it has been completely removed.

- The tumor contains hormone receptors and hormone therapy is given.

- None of the lymph nodes that were removed contained cancer.

Some women who do not meet these criteria may be tempted to avoid radiation, but studies have shown that not getting radiation increases the chances of the cancer coming back.

Adjuvant systemic therapy: Most doctors will discuss the pros and cons of adjuvant hormone therapy (either tamoxifen or an aromatase inhibitor) with all women who have a hormone receptor–positive (estrogen or progesterone) breast cancer, no matter how small the tumor. Women with tumors larger than 0.5 cm (about 1/4 inch) across may be more likely to benefit from it.

If the tumor is smaller than 1 cm (about 1/2 inch) across, adjuvant chemotherapy (chemo) is not usually offered. Some doctors may suggest chemo if a cancer smaller than 1 cm has any unfavorable features (such as being high-grade, hormone receptor–negative, HER2-positive, or having a high score on one of the gene panels). Adjuvant chemotherapy is usually recommended for larger tumors.

For HER2-positive cancers, adjuvant trastuzumab (Herceptin) is usually recommended as well.

See below for more information on adjuvant therapy.

Stage II

These cancers are larger and/or have spread to a few nearby lymph nodes.

Local therapy: Surgery and radiation therapy options for stage II tumors are similar to those for stage I tumors, except that in stage II, radiation therapy may be considered even after mastectomy if the tumor is large (more than 5 cm across) or the cancer cells are found in several lymph nodes.

Adjuvant systemic therapy: Adjuvant systemic therapy is recommended for women with stage II breast cancer. It may involve hormone therapy, chemotherapy, trastuzumab, or some combination of these, depending on the patient's age, estrogen-receptor status, and HER2/neu status. See the following section for more information on adjuvant therapy.

Neoadjuvant therapy: An option for some women who would like to have breast-conserving therapy for tumors larger than 2 cm (about 4/5 inch across) is to have neoadjuvant (before surgery) chemotherapy, hormone therapy, and/or trastuzumab to shrink the tumor.

If the neoadjuvant treatment shrinks the tumor enough, women may then be able to have breast-conserving surgery (such as lumpectomy) followed by radiation therapy, as well as hormone therapy if the tumor is hormone receptor-positive. Further chemotherapy may also be considered. If the tumor does not shrink enough for breast-conserving surgery, then mastectomy may be required. This may be followed by different chemotherapy. Radiation therapy may be needed if the tumor is large (more than 2 inches across) or if lymph nodes contain cancer. The radiation is usually given after surgery. Also, hormone therapy may be given if the tumor is hormone receptor–positive. Hormone therapy can be given both before and after surgery. A woman's chance for survival from breast cancer does not seem to be affected by whether she gets her chemotherapy before or after her breast surgery.

Stage III

Local treatment for some stage IIIA breast cancers is largely the same as that for stage II breast cancers. They may be removed by breast-conserving surgery (such as lumpectomy) followed by radiation therapy, or by modified radical mastectomy (with or without breast reconstruction). Sentinel lymph node biopsy or axillary lymph node dissection is also done. Radiation therapy may be used after mastectomy if the tumor is large (more than 5 cm across) or is found to have spread to several lymph nodes. Neoadjuvant therapy may be an option for some women who would like to have breast-conserving therapy.

Surgery is usually followed by adjuvant systemic chemotherapy, and/or hormone therapy, and/or trastuzumab.

Stage III cancers are often treated with neo adjuvant chemo (chemotherapy before surgery). Then a mastectomy is done, usually with removal of the axillary lymph nodes (an axillary lymph node dissection). Reconstruction may be done as well. Breast-conserving surgery may be an option for some women. Surgery is followed by radiation therapy, even if a mastectomy is done. Adjuvant chemotherapy may also be given, and adjuvant hormone therapy is offered to all women with hormone receptor–positive breast cancers.

Adjuvant therapy for stages I to III breast cancer

Adjuvant drug therapy may be recommended, based on the tumor's size, spread to lymph nodes, and other prognostic features. If it is, you may get chemotherapy, trastuzumab (Herceptin), hormone therapy, or some combination of these.

Hormone therapy: Hormone therapy is not likely to be effective for women with hormone receptor-negative tumors. Hormone therapy is frequently offered to all women with hormone receptor–positive invasive breast cancer regardless of the size of the tumor or the number of lymph nodes involved.

Women who are still having periods and have hormone receptor–positive tumors can be treated with tamoxifen, which blocks the effects of estrogen being made by the ovaries. Some doctors also give a luteinizing hormone-releasing hormone (LHRH) analog, which makes the ovaries temporarily stop functioning. Another (permanent) option is surgical removal of the ovaries (oophorectomy). If the woman becomes post-menopausal within 5 years of starting tamoxifen (either naturally or because her ovaries are removed), she may be switched from tamoxifen to an aromatase inhibitor.

Sometimes a woman will stop having periods after chemotherapy or while on tamoxifen. But this does not necessarily mean she is truly post-menopausal. The woman's doctor can do blood tests for certain hormones to determine her menopausal status. This is important because the aromatase inhibitors will only benefit post-menopausal women.

Women no longer having periods, or who are known to be in menopause at any age, and who have hormone receptor–positive tumors will generally get adjuvant hormone therapy

either with an aromatase inhibitor (typically for 5 years), or with tamoxifen for a few years followed by an aromatase inhibitor for a few more. For women who can't take aromatase inhibitors, an alternative is tamoxifen for 5 years.

As mentioned before, there are still many unanswered questions about the best way to use these drugs. For example, it's not clear if starting adjuvant therapy with one of these drugs is better than giving tamoxifen for some length of time and then switching to an aromatase inhibitor. Nor has the optimal length of treatment with aromatase inhibitors been determined. Studies now under way should help answer these questions. You might want to discuss these newer treatments with your doctor.

If chemotherapy is to be given as well as a general rule, hormone therapy is started after chemotherapy is completed.

Chemotherapy: Chemotherapy is usually recommended for all women with an invasive breast cancer whose tumor is hormone receptor-negative, and for women with hormone receptor-positive–tumors who may get additional benefit from having chemotherapy along with their hormone therapy, based on the stage and characteristics of their tumor.

Adjuvant chemotherapy can decrease the risk of the cancer coming back, but it does not remove the risk completely. Before deciding if it's right for you, it is important to understand the chance of your cancer returning and how much adjuvant therapy will decrease that risk.

The specific drug regimens and the length of treatment are often determined by the stage and grade of the cancer. The typical chemotherapy regimens are listed in the chemotherapy section. The length of these regimens usually ranges from 4 to 6 months. In some cases, dose dense chemotherapy may be used.

Trastuzumab (Herceptin): Women who have HER2-positive cancers are usually given trastuzumab along with chemotherapy as part of their treatment.

A common chemotherapy regimen is doxorubicin (Adriamycin) and cyclophosphamide together for about 3 months, followed by paclitaxel (Taxol) and trastuzumab. The paclitaxel is given for about 3 months, while the trastuzumab is given for about 1 year.

A concern among doctors is that giving the trastuzumab so soon after doxorubicin may lead to heart problems, so heart function is watched closely during treatment with tests such as echocardiograms.

To try to lessen the possible effects on the heart, doctors are also looking for effective chemotherapy combinations that don't contain doxorubicin. One such regimen is called *TCH.* It uses the chemotherapy drugs docetaxel (Taxotere) and carboplatin given every 3 weeks along with weekly trastuzumab (Herceptin) for 6 cycles. This is followed by trastuzumab every 3 weeks for a year.

Aids for adjuvant therapy decision making: Some doctors may use newer gene pattern tests to help decide whether to give adjuvant chemotherapy to women with certain stage I or II breast cancers. Examples of such tests include Oncotype DX® and MammaPrint®, which are described in more detail in the section "How is breast cancer diagnosed?"

These tests are done on a sample of your breast cancer tissue. They look at the function of several genes within the cancer to help predict the risk of it returning after treatment. The tests will not tell your doctor which is the best hormone therapy or chemotherapy to recommend. Clinical trials are now being done to see if these tests can really tell which women can do without adjuvant chemotherapy in situations where doctors are often uncertain, such as in women with small tumors and uninvolved lymph nodes.

For help in deciding if adjuvant therapy is right for you, you might want to visit the Mayo Clinic Web site at www.mayoclinic.com and type "adjuvant therapy for breast cancer" into the search box. You will find a page that will help you to understand the possible benefits and limits of adjuvant therapy.

Other online guides, such as www.adjuvantonline.com, are designed to be used by health care professionals. This Web site provides information about your risk of the cancer returning within the next 10 years and what benefits you might expect from hormone therapy and/or chemotherapy. You may want to ask your doctor if he or she uses this site.

Stage IV

Stage IV cancers have spread beyond the breast and lymph nodes to other parts of the body. Although surgery and/or radiation may be useful in some situations (see below), they are very unlikely to cure these cancers, so systemic therapy is the main treatment. Depending on many factors, this may consist of hormone therapy, chemotherapy, targeted therapies like trastuzumab (Herceptin) or lapatinib (Tykerb), or some combination of these treatments.

Trastuzumab may help women with HER2-positive cancers live longer if it is given with the first chemotherapy for stage IV disease. It is not yet known whether it also should be given at the same time as hormone therapy, or how long a woman should remain on therapy.

All of the systemic therapies given for breast cancer -- hormone therapy, chemotherapy, and the newer targeted therapies -- have potential side effects, which were described in previous sections. Your doctor will explain to you the benefits and risks of these treatments before prescribing them.

Radiation therapy and/or surgery may also be used in certain situations, such as to treat a small number of metastases in a certain area, to prevent bone fractures or blockage in the liver, or to provide relief of pain or other symptoms. If your doctor recommends such local treatments, it is important that you understand their goal -- whether it is to try to cure the cancer or to prevent or treat symptoms.

In some cases, regional chemotherapy (where drugs are delivered directly into a certain area, such as the fluid around the brain) may be useful as well.

Treatment to relieve symptoms depends on where the cancer has spread. For example, pain from bone metastases may be treated with external beam radiation therapy and/or bisphosphonates such as pamidronate (Aredia) or zoledronic acid (Zometa). Most doctors recommend bisphosphonates (along with calcium and vitamin D) for all patients whose

breast cancer has spread to their bones. (For more information about treatment of bone metastases, see our document, *Bone Metastasis*.)

Advanced cancer that progresses during treatment: Treatment for advanced breast cancer can often shrink or slow the growth of the cancer (often for many years), but it may stop working after a time. Further treatment at this point depends on several factors, including previous treatments, where the cancer is located, and a woman's age, general health, and desire to continue getting treatment.

For hormone receptor–positive cancers that were being treated with hormone therapy, switching to another type of hormone therapy is sometimes helpful. If not, chemotherapy is usually the next step.

For cancers that are no longer responding to one chemotherapy regimen, trying another may be helpful. There are many different drugs and combinations that can be used to treat breast cancer. However, each time a cancer progresses during treatment it becomes less likely that further treatment will have an effect.

HER2-positive cancers that no longer respond to trastuzumab may respond to lapatinib (Tykerb), another drug that attacks the HER2 protein. This drug is usually given along with the chemotherapy drug capecitabine (Xeloda). Both of these drugs are taken as pills.

Because current treatments are very unlikely to cure advanced breast cancer, patients in otherwise good health are encouraged to think about taking part in clinical trials of other promising treatments.

Recurrent breast cancer

Cancer is called recurrent when it come backs after treatment. Recurrence can be local (in the same breast or near the mastectomy scar) or in a distant area. Cancer that is found in the opposite breast is not a recurrence -- it is a new cancer that requires its own treatment.

Local recurrence: Treatment of women whose breast cancer has recurred locally depends on their initial treatment. If the woman had breast-conserving therapy, local recurrence in the breast is usually treated with mastectomy. If the initial treatment was mastectomy, recurrence near the mastectomy site is treated by removing the tumor whenever possible. This is followed by radiation therapy, but only if none had been given after the original surgery. (Radiation can't be given to the same area twice.) In either case, hormone therapy, trastuzumab, chemotherapy, or some combination of these may be used after surgery and/or radiation therapy.

Distant recurrence: In general, women who have a recurrence involving organs like the bones, lungs, brain, etc., are treated the same way as those found to have stage IV breast cancer in these organs when they were first diagnosed (see treatment for stage IV). The only difference is that treatment may be affected by previous treatments a woman has had.

Should your cancer come back, our document, *When Your Cancer Comes Back: Cancer Recurrence* can provide you with more general information on how to manage and cope with this phase of your treatment.

Treatment of breast cancer during pregnancy

Breast cancer is diagnosed in about 1 pregnant woman out of 3,000. In general, treatment recommendations depend upon how long the woman has been pregnant.

Radiation therapy during pregnancy is known to increase the risk of birth defects, so it is not recommended for pregnant women with breast cancer. For this reason, breast-conserving therapy (lumpectomy and radiation therapy) is only an option if treatment can wait until it is safe to deliver the baby. But breast biopsy procedures and even modified radical mastectomy are safe for the mother and fetus.

For a long time it was assumed that chemotherapy was dangerous to the fetus. But several recent studies have found that using certain chemotherapy drugs during the second and third trimesters (the fourth to ninth months) does not increase the risk of birth defects. Because of concern about the potential damage to the fetus, the safety of chemotherapy during the first trimester (the first 3 months) of pregnancy has not been studied.

Hormone therapy may affect the fetus and should not be started until after the patient has given birth.

Many chemotherapy and hormone therapy drugs can enter breast milk and could be passed on to the baby, so breast-feeding is not usually recommended during chemotherapy or hormone therapy.

For more information, see our document, *Pregnancy and Breast Cancer*.

More treatment information

For more details on treatment options -- including some that may not be addressed in this document -- the National Cancer Institute (NCI) and the National Comprehensive Cancer Network (NCCN) are good sources of information.

The NCI provides treatment guidelines via its telephone information center (1-800-4-CANCER) and its Web site (www.cancer.gov). Detailed guidelines intended for use by cancer care professionals are also available on www.cancer.gov.

The NCCN, made up of experts from many of the nation's leading cancer centers, develops cancer treatment guidelines for doctors to use when treating patients. Those are available on the NCCN Web site (www.nccn.org).

What should you ask your doctor about breast cancer?

It is important for you to have frank, open discussions with your cancer care team. Don't be afraid to ask questions, no matter how minor you might think they are. Some questions to consider:

- What type of breast cancer do I have? How does this affect my treatment options and prognosis?

- Has my cancer spread to lymph nodes or internal organs?

- What is the stage of my cancer and how does it affect my treatment options and outlook?

- Are there other tests that need to be done before we can decide on treatment?

- Should I consider genetic testing?

- Should I think about taking part in a clinical trial?

- What treatments are appropriate for me? What do you recommend? Why?

- What are the risks and side effects that I should expect?

- How effective will breast reconstruction surgery be if I need or want it?

- What are the pros and cons of having it done right away or waiting until later?

- What will my breasts look and feel like after my treatment? Will I have normal sensation in them?

- How long will treatment last? What will it involve? Where will it be done?

- What should I do to get ready for treatment?

- Will I need a blood transfusion?

- Should I follow a special diet or make other lifestyle changes?

- What are the chances my cancer will come back with the treatment programs we have discussed? What would we do if that happens?

- Will I go through menopause as a result of the treatment?

- Will I be able to have children after my treatment?

- What type of follow-up will I need after treatment?

Be sure to write down any questions that occur to you that are not on this list. For instance, you might want specific information about recovery times so that you can plan your work schedule. Or you may want to ask about second opinions. Taking another

person and/or a tape recorder to the appointment can be helpful. Collecting copies of your medical records, pathology reports, and radiology reports may be useful in case you wish to seek a second opinion at a later time.

What happens after treatment for breast cancer?

Completing treatment can be both stressful and exciting. You will probably be relieved to finish treatment, yet it is hard not to worry about cancer coming back. (When cancer returns, it is called recurrence.) This is a very common concern among those who have had cancer. For more information on this please refer to our document, *Living with Uncertainty: The Fear of Cancer Recurrence*.

It may take a while before your confidence in your own recovery begins to feel real and your fears are somewhat relieved. Even with no recurrences, people who have had cancer learn to live with uncertainty.

Follow-up care

After treatment is completed, it is very important to go to all scheduled follow-up appointments. During these visits, your doctors will ask questions about any symptoms and may do physical exams and order lab tests or imaging tests as needed to look for recurrences or side effects. Almost any cancer treatment can have side effects. Some may last for a few weeks to several months, but others can be permanent. You should never hesitate to tell your doctor or other members of your cancer care team about any symptoms or side effects that concern you.

At first, your follow-up appointments will probably be scheduled for every 3 to 6 months. The longer you have been free of cancer, the less often the appointments are needed. After 5 years, they are typically done about once a year. If you had breast-conserving surgery, you will need to continue to have mammograms every year.

If you are taking tamoxifen, you should have yearly pelvic exams because this drug can increase your risk of uterine cancer. Be sure to tell your doctor right away about any abnormal vaginal bleeding you are having. Although this is usually caused by a non-cancerous condition, it may also be the first sign of uterine cancer.

If you are taking an aromatase inhibitor, you may be at increased risk for thinning of the bones. Your doctor will want to monitor your bone health and may consider testing your bone density.

Other tests such as blood tumor marker studies, blood tests of liver function, bone scans, and chest x-rays are not usually needed unless symptoms or physical exam findings suggest it is likely the cancer has recurred. These and other tests may be done as part of evaluating new treatments by clinical trials.

If exams and tests suggest a recurrence, imaging tests such as an x-ray, CT scan, PET scan, MRI scan, bone scan, and/or a biopsy may be done. Your doctor may also measure levels of blood tumor markers such as CA-15-3, CA 27-29, or CEA. The blood levels of these substances go up in some women if their cancer has spread to bones or other organs such as the liver. They are not elevated in all women with recurrence, so they aren't always helpful. If they are elevated, they may help your doctor monitor the results of therapy.

If cancer does recur, the treatment will depend on the location of the cancer and what treatments you've had before. It may involve surgery, radiation therapy, hormone therapy, chemotherapy, targeted therapy, or some combination of these. For more information on how recurrent cancer is treated, see the section, "How is breast cancer treated?" For more general information on dealing with a recurrence, you may also want to see our document, *When Your Cancer Comes Back: Cancer Recurrence*.

Lymphedema

Lymphedema, or swelling of the arm from buildup of fluid, may occur any time after treatment for breast cancer. Any treatment that involves axillary lymph node dissection or radiation to the axillary lymph nodes carries the risk of lymphedema because normal drainage of lymph fluid from the arm is changed.

One of the first symptoms of lymphedema may be a feeling of tightness in the arm or hand on the same side that was treated for breast cancer. Any swelling, tightness, or injury to the arm or hand should be reported promptly to your doctor or nurse.

There is no good way to predict who will and will not develop lymphedema. It can occur right after surgery, or months, or even years later. The possibility of developing lymphedema remains throughout a woman's lifetime.

With care, lymphedema can often be avoided or, if it develops, kept under control. Injury or infection involving the affected arm or hand can contribute to the development of lymphedema or make existing lymphedema worse, so preventive measures should focus on protecting the arm and hand. Most doctors recommend that women avoid having blood drawn from or blood pressures taken on the arm on the side of the lymph node surgery or radiation.

To learn more, see our document, *Lymphedema: What Every Woman with Breast Cancer Should Know*.

Quality of life

Women who have had treatment for breast cancer should be reassured that while they may be left with reminders of their treatment (such as surgical scars), their overall quality of life, once treatment has been completed, can be normal. Extensive studies have shown this. Women who have had chemotherapy may, however, notice a slight decrease in certain areas of function.

Some studies suggest that younger women, who represent about 1 out of 4 breast cancer survivors, tend to have more problems adjusting to the stresses of breast cancer and its treatment. They may have more trouble with emotional and social functioning. Some can feel isolated. For some women, chemotherapy may have caused early menopause, which can be very distressing on its own. There may also be sexual difficulties. These issues may be helped with counseling and support groups directed to younger breast cancer survivors.

Emotional aspects of breast cancer

It is important that your focus on tests and treatments does not prevent you from considering your emotional, psychological, and spiritual health as well. Once your treatment ends, you may find yourself overwhelmed by emotions. This happens to a lot of people. You may have been going through so much during treatment that you could only focus on getting through your treatment.

Now you may find that you think about the potential of your own death, or the effect of your cancer on your family, friends, and career. You may also begin to re-evaluate your relationship with your spouse or partner. Unexpected issues may also cause concern -- for instance, as you become healthier and have fewer doctor visits, you will see your health care team less often. That can be a source of anxiety for some.

This is an ideal time to seek out emotional and social support. You need people you can turn to for strength and comfort. Support can come in many forms: family, friends, cancer support groups, church or spiritual groups, online support communities, or individual counselors.

Almost everyone who has been through cancer can benefit from getting some type of support. What's best for you depends on your situation and personality. Some people feel safe in peer-support groups or education groups. Others would rather talk in an informal setting, such as church. Others may feel more at ease talking one-on-one with a trusted friend or counselor. Whatever your source of strength or comfort, make sure you have a place to go with your concerns.

The cancer journey can feel very lonely. It is not necessary or realistic to go it all by yourself. And your friends and family may feel shut out if you decide not to include them. Let them in -- and let in anyone else who you feel may help. If you aren't sure who can help, call your American Cancer Society at 1-800-227-2345 and we can put you in touch with an appropriate group or resource.

Body image

Along with having to cope with the emotional stress that cancer and its treatment can cause, many women with breast cancer also find themselves dealing with changes in their appearance as a result of their treatment.

Some changes may be short term, such as hair loss. But even short-term changes can have a profound effect on how a woman feels about herself. A number of options are

available to help women cope with hair loss, including wigs, hats, scarves, and other accessories. For a list of some companies that sell wigs and other hair accessories, see our document, *Breast Prostheses and Hair Loss Accessories List*. Alternatively, some women may choose to use their baldness as a way to identify themselves as breast cancer survivors.

Other changes that result from breast cancer treatment may be more permanent, like the loss of part or all of a breast (or breasts) after surgery. Some women may choose reconstructive surgery to address this, while others may opt for a breast form.

Regardless of the changes you may experience, it's important to know that there is advice and support out there to help you cope with these changes. Speaking with your doctor or other members of your health care team is often a good starting point. There are also many support groups available, such as the American Cancer Society's Reach to Recovery program. Call 1-800-227-2345 to learn more about programs in your area.

Breast forms and bras vs. breast reconstruction

Following a mastectomy (or breast-conserving surgery in some cases), a woman may consider having the breast mound rebuilt, or reconstructed. This is usually something that is discussed before surgery to treat the cancer. Decisions about the type of reconstruction and when it will be done depend on each woman's medical situation and personal preferences. There are several types of reconstructive surgery available. Some use saline (salt water) or silicone implants, while others use tissues from other parts of your body.

For a discussion of the different breast reconstruction options, see our document, *Breast Reconstruction After Mastectomy*.

A *breast form* is a prosthesis (artificial body part) worn either inside a bra or attached to the body to simulate the appearance and feel of a natural breast. For women who have had a mastectomy, breast forms can be an important alternative to breast reconstruction. Some women may not want further surgery, knowing that breast reconstruction can sometimes require several procedures to complete.

If you are planning on using a breast form, your doctor will tell you when you have healed enough to be fitted for a permanent breast form or prosthesis. Most of these forms are made from materials that mimic the movement, feel, and weight of natural tissue. A properly weighted form provides the balance your body needs for correct posture and anchors your bra, keeping it from riding up.

At first, these forms may feel too heavy, but in time they will feel natural. Prices vary considerably. High price doesn't necessarily mean that the product is the best for you. Take time to shop for a good fit, comfort, and an attractive, natural appearance in the bra and under clothing. Your clothes should fit the way they did before surgery.

The right bra for you may very well be the one you have always worn. It may or may not need adjustments. If there is tenderness during healing, a bra extender can help by increasing the circumference of the bra so that it does not bind the chest too tightly.

Heavy-breasted women can relieve pressure on shoulder straps by slipping a bra shoulder pad under one or both straps.

If you decide to wear your breast form in a pocket in your bra, you can have your regular bra adapted. There are also special mastectomy bras with the pockets already sewn in. If the breast form causes any kind of skin irritation, use a bra with a pocket. If your bra has underwires, you may be able to wear it, but be sure to clear this with your doctor.

You might want to wear your prosthesis under nightgowns but would like something more comfortable than a regular bra. Most department stores carry a soft bra, sometimes called a leisure or night bra.

For a list of companies that sell breast prostheses and other accessories, see our document, *Breast Prostheses and Hair Loss Accessories List.*

Insurance coverage of breast prostheses can vary. Be sure to read your insurance policy to see what is covered and how you must submit claims. Also, ask your doctor to write prescriptions for your prosthesis and for any special mastectomy bras. When purchasing bras or breast forms, mark the bills and any checks you write "surgical." Medicare and Medicaid can be used to pay for some of these expenses if you are eligible. The cost of breast forms and bras with pockets may be tax deductible, as may the cost if you have a bra altered. Keep careful records of all related expenses.

Be aware that some insurance companies will not cover both a breast prosthesis and reconstructive surgery. That can mean that if you submit a claim for a prosthesis or bra to your insurance company, in some cases the company **will not** cover reconstruction, should you choose this procedure in the future. Make sure you get all the facts before submitting any insurance claims.

Be sure to call your local ACS Reach to Recovery volunteer about any questions you have. She will give you suggestions, additional reading material, and advice. Remember that she's been there and will probably understand.

Sexuality

Concerns about sexuality are often very worrisome to a woman with breast cancer. Several factors may place a woman at higher risk for sexual problems after breast cancer. Physical changes (such as those after surgery) may make a woman less comfortable with her body. Some treatments for breast cancer, such as chemotherapy, can change a woman's hormone levels and may negatively affect sexual interest and/or response. A diagnosis of breast cancer when a woman is in her 20s or 30s can be especially difficult because choosing a partner and childbearing are often very important during this period.

Suggestions that may help a woman adjust to changes in her body image include looking at and touching herself; seeking the support of others, preferably before surgery; involving her partner as soon as possible after surgery; and openly communicating feelings, needs, and wants created by her changed image.

Sexual impact of surgery and radiation

The most common sexual side effects stem from damage to a woman's feelings of attractiveness. In our culture, we are taught to view breasts as a basic part of beauty and femininity. If her breast has been removed, a woman may be insecure about whether her partner will accept her and find her sexually pleasing.

The breasts and nipples are also sources of sexual pleasure for many women. Touching the breasts is a common part of foreplay in our culture. For many women, breast stimulation adds to sexual excitement.

Treatment for breast cancer can interfere with pleasure from breast caressing. After a mastectomy, the whole breast is gone. Some women still enjoy being stroked around the area of the healed scar. Others dislike being touched there and may no longer even enjoy being touched on the remaining breast and nipple. Some women who have had a mastectomy may feel self-conscious in sex positions where the area of the missing breast is more visible.

Breast surgery or radiation to the breasts does not physically decrease a woman's sexual desire. Nor does it decrease her ability to have vaginal lubrication or normal genital feelings, or to reach orgasm. Some good news from recent research is that within a year after their surgery, most women with early stage breast cancer have good emotional adjustment and sexual satisfaction. They report a quality of life similar to women who never had cancer.

A few women have chronic pain in their chests and shoulders after radical mastectomy. During intercourse, supporting these areas with pillows and avoiding positions where your weight rests on your chest or arms may help.

If surgery removed only the tumor (segmental mastectomy or lumpectomy) and was followed by radiation therapy, the breast may be scarred. It also may be a different shape or size. During radiation therapy, the skin may become red and swollen. The breast also may be a little tender. Feeling in the breast and nipple, however, should return to normal.

Sexual impact of breast reconstruction

Breast reconstruction restores the shape of the breast, but it cannot restore normal breast sensation. The nerve that supplies feeling to the nipple runs through the deep breast tissue, and it gets disconnected during surgery. In a reconstructed breast, the feeling of pleasure from touching the nipple is lost. A rebuilt nipple has much less feeling.

In time, the skin on the reconstructed breast will regain some sensitivity but probably will not give the same kind of pleasure as before mastectomy. Breast reconstruction often makes women more comfortable with their bodies, however, and helps them feel more attractive.

Effect on your partner

Relationship issues are also important because the cancer diagnosis can be very distressing for the partner, as well as the patient. Partners are usually concerned about how to express their love physically and emotionally after treatment, especially surgery. Breast cancer can be a growth experience for couples under certain circumstances. The

relationship may be enhanced if the partner takes part in decision making and accompanies the woman to surgery and other treatments.

Pregnancy after breast cancer

Because of the well-established link between estrogen levels and growth of breast cancer cells, many doctors have advised breast cancer survivors not to become pregnant for at least 2 years after treatment. This would allow any early return of the cancer to be diagnosed, which in turn could affect a woman's decision to become pregnant. But this 2-year wait period is not based on strong scientific evidence, and earlier pregnancy may not be harmful. Although few studies have been done, nearly all have found that pregnancy does not increase the risk of recurrence after successful treatment of breast cancer.

Women are advised to discuss their risk of recurrence with their doctors. In some cases, counseling can help women with the complex issues and uncertainties about motherhood and breast cancer survivorship.

Post-menopausal hormone therapy after breast cancer

The known link between estrogen levels and breast cancer growth has discouraged many women and their doctors from choosing or recommending post-menopausal hormone therapy (PHT), also called hormone replacement therapy (HRT), to help relieve menopausal symptoms. Unfortunately, many women experience menopausal symptoms after treatment for breast cancer. This can occur naturally, as a result of post-menopausal women stopping PHT, or in pre-menopausal women as a result of chemotherapy or ovarian ablation. Tamoxifen can also cause menopausal symptoms such as hot flashes.

In the past, doctors have offered PHT after breast cancer treatment to women suffering from severe symptoms because early studies had shown no harm. But a well-designed clinical trial (the HABITS study) found that breast cancer survivors taking PHT were much more likely to develop a new or recurrent breast cancer than women who were not taking the drugs. This is why most doctors now feel that for women previously treated for breast cancer, taking PHT would be unwise.

Women may want to discuss with their doctors alternatives to PHT to help with specific menopausal symptoms. Some doctors have suggested that phytoestrogens (estrogen-like substances from certain plant sources, such as soy products) may be safer than the estrogens used in PHT. However, there is not enough information available on phytoestrogens to fully evaluate their safety for breast cancer survivors.

Drugs without hormonal properties that may be somewhat effective in treating hot flashes include the antidepressant venlafaxine (Effexor®), the blood pressure drug clonidine, and the nerve drug gabapentin (Neurontin®). Acupuncture also seems to be helpful in treating hot flashes. For women taking tamoxifen, it's important to note that some antidepressants, known as SSRIs, may interact with tamoxifen and make it less effective. Ask your doctor about any possible interactions between tamoxifen and any drugs you may be taking.

Seeing a new doctor

At some point after your cancer diagnosis and treatment, you may find yourself in the office of a new doctor. Your original doctor may have moved or retired, or you may have moved or changed doctors for some reason. It is important that you be able to give your new doctor the exact details of your diagnosis and treatment. Make sure you have the following information handy:

- A copy of your pathology report(s) from any biopsy or surgery

- If you had surgery, a copy of your operative report(s)

- If you were hospitalized, a copy of the discharge summary that doctors must prepare when patients are sent home

- If you had radiation therapy, a copy of your treatment summary

- If you had systemic therapy (hormone therapy, chemotherapy, or targeted therapies), a list of your drugs, drug doses, and when you took them

It is also important to keep medical insurance. Even though no one wants to think of their cancer coming back, it is always a possibility. If it happens, the last thing you want is to have to worry about paying for treatment.

Lifestyle changes to consider during and after treatment

You can't change the fact that you have had cancer. What you can change is how you live the rest of your life -- making healthy choices and feeling as well as possible, physically and emotionally. Having cancer and dealing with treatment can be time-consuming and emotionally draining, but it can also be a time to look at your life in new ways. Maybe you are thinking about how to improve your health over the long term. Some people even begin this process during cancer treatment.

Make healthier choices

Think about your life before you learned you had cancer. Were there things you did that might have made you less healthy? Maybe you drank too much alcohol, or ate more than you needed, or smoked, or didn't exercise very often. Emotionally, maybe you kept your feelings bottled up, or maybe you let stressful situations go on too long.

Now is not the time to feel guilty or to blame yourself. However, you can start making changes today that can have positive effects for the rest of your life. Not only will you feel better but you will also be healthier. What better time than now to take advantage of the motivation you have as a result of going through a life-changing experience like having cancer?

You can start by working on those things that you feel most concerned about. Get help with those that are harder for you. For instance, if you are thinking about quitting smoking and need help, call 1-800-227-2345.

Diet and nutrition

Eating right can be a challenge for anyone, but it can get even tougher during and after cancer treatment. For instance, treatment often may change your sense of taste. Nausea can be a problem. You may lose your appetite for a while and lose weight when you don't want to. On the other hand, some people gain weight even without eating more. This can be frustrating, too.

If you are losing weight or have taste problems during treatment, do the best you can with eating and remember that these problems usually improve over time. You may want to ask your cancer team for a referral to a dietitian, an expert in nutrition who can give you ideas on how to fight some of the side effects of your treatment. You may also find it helps to eat small portions every 2 to 3 hours until you feel better and can go back to a more normal schedule.

One of the best things you can do after treatment is to put healthy eating habits into place. You will be surprised at the long-term benefits of some simple changes, like increasing the variety of healthy foods you eat. Try to eat 5 or more servings of vegetables and fruits each day. Choose whole grain foods instead of white flour and sugars. Try to limit meats that are high in fat. Cut back on processed meats like hot dogs, bologna, and bacon. Get rid of them altogether if you can. If you drink alcohol, limit yourself to 1 or 2 drinks a day at the most. And don't forget to get some type of regular exercise. The combination of a good diet and regular exercise will help you maintain a healthy weight and keep you feeling more energetic.

Weight

For a woman diagnosed with breast cancer, achieving or maintaining a desirable weight may be one of the most important things you can do. Most studies have found that women who are overweight or obese when they are first diagnosed are more likely to have their disease recur and are more likely to die from breast cancer. Overweight women should be encouraged to lose weight after treatment. In some cases, a modest weight loss program may even be started during treatment, if the doctor approves.

Study results have been mixed as to how strongly weight gain affects breast cancer recurrence or survival. Some studies have found that those who gained significant amounts of weight after diagnosis were more likely to relapse and more likely to die than were women who gained less weight. However, other recent studies have not found that weight gain affected prognosis.

Rest, fatigue, work, and exercise

Fatigue is a very common symptom in people being treated for cancer. This is often not an ordinary type of tiredness but a "bone-weary" exhaustion that doesn't get better with rest. For some, this fatigue lasts a long time after treatment, and can discourage them from physical activity.

However, exercise can actually help you reduce fatigue. Studies have shown that patients who follow an exercise program tailored to their personal needs feel physically and emotionally improved and can cope better.

If you are ill and need to be on bed rest during treatment, it is normal to expect your fitness, endurance, and muscle strength to decline some. Physical therapy can help you maintain strength and range of motion in your muscles, which can help fight fatigue and the sense of depression that sometimes comes with feeling so tired.

Any program of physical activity should fit your own situation. An older person who has never exercised will not be able to take on the same amount of exercise as a 20-year-old who plays tennis 3 times a week. If you haven't exercised in a few years but can still get around, you may want to think about taking short walks.

Talk with your health care team before starting, and get their opinion about your exercise plans. Then, try to get an exercise buddy so that you're not doing it alone. Having family or friends involved when starting a new exercise program can give you that extra boost of support to keep you going when the push just isn't there.

If you are very tired, though, you will need to balance activity with rest. It is okay to rest when you need to. It is really hard for some people to allow themselves to do that when they are used to working all day or taking care of a household. Exercise can improve your physical and emotional health.

- It improves your cardiovascular (heart and circulation) fitness.

- It strengthens your muscles.

- It reduces fatigue.

- It lowers anxiety and depression.

- It makes you feel generally happier.

- It helps you feel better about yourself.

And long term, we know that exercise plays a role in preventing some cancers. The American Cancer Society, in its guidelines on physical activity for cancer prevention, recommends that to reduce the risk for developing breast cancer, women should take part in moderate to vigorous physical activity for 45 to 60 minutes on 5 or more days of the week. Moderate activities are those that take about as much effort as a brisk walk. Vigorous activities use larger muscle groups, make you sweat, and cause a noticeable increase in heart rate and breathing.

The role of physical activity in reducing the risk of breast cancer recurrence is less well-defined, although several recent studies suggest that breast cancer survivors who are physically active may have lower rates of recurrence and death than those who are inactive.

What happens if treatment is no longer working?

If cancer continues to grow after one kind of treatment, or if it returns, it is often possible to try another treatment plan that might still cure the cancer, or at least shrink the tumors enough to help you live longer and feel better. On the other hand, when a person has received several different medical treatments and the cancer has not been cured, over time the cancer tends to become resistant to all treatment. At this time it's important to weigh the possible limited benefit of a new treatment against the possible downsides, including continued doctor visits and treatment side effects.

Everyone has his or her own way of looking at this. Some people may want to focus on remaining comfortable during their limited time left.

This is likely to be the most difficult time in your battle with cancer -- when you have tried everything medically within reason and it's just not working anymore. Your doctor may offer you new treatment, but you need to consider that at some point, continuing treatment is not likely to improve your health or change your prognosis or survival.

If you want to continue treatment to fight your cancer as long as you can, you still need to consider the odds of more treatment having any benefit. In many cases, your doctor can estimate the response rate for the treatment you are considering. Some people are tempted to try more chemotherapy or radiation, for example, even when their doctors say that the odds of benefit are less than 1%. In this situation, you need to think about and understand your reasons for choosing this plan.

No matter what you decide to do, it is important that you be as comfortable as possible. Make sure you are asking for and getting treatment for any symptoms you might have, such as pain. This type of treatment is called *palliative treatment*.

Palliative treatment helps relieve these symptoms, but is not expected to cure the disease; its main purpose is to improve your quality of life. Sometimes, the treatments you get to control your symptoms are similar to the treatments used to treat cancer. For example, radiation therapy might be given to help relieve bone pain from bone metastasis. Or chemotherapy might be given to help shrink a tumor and keep it from causing a bowel obstruction. But this is not the same as receiving treatment to try to cure the cancer.

At some point, you may benefit from hospice care. Most of the time, this is given at home. Your cancer may be causing symptoms or problems that need attention, and hospice focuses on your comfort. You should know that receiving hospice care doesn't mean you can't have treatment for the problems caused by your cancer or other health conditions. It just means that the focus of your care is on living life as fully as possible and feeling as well as you can at this difficult stage of your cancer.

Remember also that maintaining hope is important. Your hope for a cure may not be as bright, but there is still hope for good times with family and friends -- times that are filled with happiness and meaning. In a way, pausing at this time in your cancer treatment is an opportunity to refocus on the most important things in your life. This is the time to do some things you've always wanted to do and to stop doing the things you no longer want to do.

What's new in breast cancer research and treatment?

Research into the causes, prevention, and treatment of breast cancer is under way in many medical centers throughout the world.

Causes of breast cancer

Studies continue to uncover lifestyle factors and habits that alter breast cancer risk. Ongoing studies are looking at the effect of exercise, weight gain or loss, and diet on breast cancer risk.

Studies on the best use of genetic testing for BRCA1 and BRCA2 mutations continue at a rapid pace. Scientists are also exploring how common gene variations may affect breast cancer risk. Each gene variant has only a modest effect in risk (10 to 20%), but when taken together they may potentially have a large impact.

Potential causes of breast cancer in the environment have also received more attention in recent years. While much of the science on this topic is still in its earliest stages, this is an area of active research.

A large, long-term study funded by the National Institute of Environmental Health Sciences (NIEHS) is now being done to help find the causes of breast cancer. Known as the Sister Study, it has enrolled 50,000 women who have sisters with breast cancer. This study will follow these women for at least 10 years and collect information about genes, lifestyle, and environmental factors that may cause breast cancer. An offshoot of the Sister Study, the Two Sister Study, is designed to look at possible causes of early onset breast cancer. To find out more about these studies, call 1-877-4-SISTER (1-877-474-7837) or visit the Sister Study Web site (www.sisterstudy.org).

Chemoprevention

Results of several studies suggest that selective estrogen-receptor modulators (SERMs) like tamoxifen and raloxifene may lower breast cancer risk in women with certain breast cancer risk factors. But so far, many women are reluctant to take these medicines because they are concerned about possible side effects.

Newer studies are looking at whether aromatase inhibitors -- drugs such as anastrozole, letrozole, and exemestane -- can reduce the risk of developing breast cancer in post-menopausal women. These drugs are already being used as adjuvant hormone therapy to help prevent breast cancer recurrences, but none of them is approved for reducing breast cancer risk at this time.

Fenretinide, a retinoid, is also being studied as a way to reduce the risk of breast cancer (retinoids are drugs related to vitamin A). In a small study, this drug reduced breast cancer risk as much as tamoxifen. Other drugs are also being studied to reduce the risk of breast cancer.

For more information, see our document, *Medicines to Reduce Breast Cancer Risk.*

New laboratory tests

Gene expression studies

One of the dilemmas with early-stage breast cancer is that doctors cannot always accurately predict which women have a higher risk of cancer coming back after treatment. That is why almost every woman, except for those with small tumors, receives some sort of adjuvant treatment after surgery. To try to better pick out who will need adjuvant therapy, researchers have looked at many aspects of breast cancers.

In recent years, scientists have been able to link certain patterns of genes with more aggressive cancers -- those that tend to come back and spread to distant sites. Some lab tests based on these findings, such as the Oncotype DX and MammaPrint tests, are already available, although doctors are still trying to determine the best way to use them. These tests are explained in the section, "How is breast cancer diagnosed?" Other tests are being developed as well.

Classifying breast cancer

Research on patterns of gene expression has also suggested some newer ways of classifying breast cancers. The current types of breast cancer are based largely on how tumors look under a microscope. A newer classification, based on molecular features, may be better able to predict prognosis and response to several types of breast cancer treatment. The new research suggests there are 4 basic types of breast cancers:

Luminal A and luminal B types: The luminal types are estrogen receptor (ER)–positive, usually low grade, and tend to grow fairly slowly. The gene expression patterns of these cancers are similar to normal cells that line the breast ducts and glands (the lining of a duct or gland is called its lumen). Luminal A cancers have the best prognosis. Luminal B cancers generally grow somewhat faster than the luminal A cancers and their outlook is not quite as good.

HER2 type: These cancers have extra copies of the HER2 gene and several other genes. They usually have a high-grade appearance under the microscope. These cancers tend to grow more quickly and have a worse prognosis, although they often can be treated successfully with targeted therapies such as trastuzumab (Herceptin) and lapatinib (Tykerb).

Basal type: Most of these cancers are of the so-called *triple-negative* type, that is, they lack estrogen or progesterone receptors and have normal amounts of HER2. The gene expression patterns of these cancers are similar to cells in the deeper basal layers of breast ducts and glands. This type is more common among women with BRCA1 gene mutations. For reasons that are not well understood, this cancer is also more common among younger and African-American women.

These are high-grade cancers that tend to grow quickly and have a poor outlook. Hormone therapy and anti-HER2 therapies like trastuzumab and lapatinib are not effective against these cancers, although chemotherapy can be helpful. A great deal of research is being done to find better ways to treat these cancers.

It is hoped that these new breast cancer classifications might someday allow doctors to better tailor breast cancer treatments, but more research is needed in this area before this is possible.

Tests of HER2 status

Determining a breast cancer's HER2 status is important to get an idea of how aggressive the cancer might be and to find out if certain drugs that target HER2 can be used to treat the disease.

Two types of tests -- immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) -- are currently used to determine HER2 status. The FISH test is generally thought to be more accurate, but it also requires special equipment, which can make testing more expensive.

A newer type of test, known as chromogenic in situ hybridization (CISH), works similarly to FISH, by using small DNA probes to count the number of HER2 genes in breast cancer cells. But this test looks for color changes (not fluorescence) and doesn't require a special microscope, which may make it less expensive. Unlike other tests, it can be used on tissue samples that have been stored in the lab. Right now, it is not being used as much as IHC or FISH.

Circulating tumor cells

Researchers have found that in many women with breast cancer, cells may break away from the tumor and enter the blood. These circulating tumor cells can be detected with sensitive lab tests. These tests are not yet available for general use, but they may eventually be helpful in determining whether treatment (such as chemotherapy) is working or in detecting cancer recurrence after treatment.

Newer imaging tests

Several newer imaging methods are now being studied for evaluating abnormalities that may be breast cancers.

Scintimammography (molecular breast imaging)

In scintimammography, a slightly radioactive tracer called technetium sestamibi is injected into a vein. The tracer attaches to breast cancer cells and is detected by a special camera.

This is a newer technique that is still being studied to see if it will be useful in finding breast cancers. Some radiologists believe it may helpful in looking at suspicious areas

found by regular mammograms, but its exact role remains unclear. Current research is aimed at improving the technology and evaluating its use in specific situations such as in the dense breasts of younger women. Some early studies have suggested that it may be almost as accurate as more expensive magnetic resonance imaging (MRI) scans. This test, however, will not replace your usual screening mammogram.

Tomosynthesis (3D mammography)

This technology is basically an extension of a digital mammogram. For this test, a woman lies face down on a table with a hole for the breast to hang through, and a machine takes x-rays as it rotates around the breast. Tomosynthesis allows the breast to be viewed as many thin slices, which can be combined into a 3-dimensional picture. It may allow doctors to detect smaller lesions or ones that would otherwise be hidden with standard mammograms. This technology is still considered experimental and is not yet available outside of a clinical trial.

Several other experimental imaging methods, including thermal imaging (thermography) are discussed in our document, *Mammograms and Other Breast Imaging Procedures*.

Treatment

Oncoplastic surgery

Breast-conserving therapy (lumpectomy or partial mastectomy) can often be used for early-stage breast cancers. But in some women, it can result in breasts of different sizes and/or shapes. For larger tumors, it might not even be possible, and a mastectomy might be needed instead. Some doctors address this problem by combining cancer surgery and plastic surgery techniques, known as oncoplastic surgery. This typically involves reshaping the breast at the time of the initial breast-conserving surgery, and may mean operating on the other breast as well to make them more symmetrical. This approach is still fairly new, and not all doctors are comfortable with it.

Breast reconstruction surgery

The number of women with breast cancer choosing breast conservation therapy has been steadily increasing, but there are some women who, for medical or personal reasons, choose mastectomy. Some of them also choose to have reconstructive surgery to restore the breast's appearance.

Technical advances in microvascular surgery (reattaching blood vessels) have made free-flap procedures an option for breast reconstruction. For more information on the types of reconstructive surgery now available, see our document, *Breast Reconstruction After Mastectomy*.

For several years, concern over a possible link between breast implants and immune system diseases has discouraged some women from choosing implants as a method of breast reconstruction. Recent studies have found that although implants can cause some

side effects (such as firm or hard scar tissue formation), women with implants do not have any greater risk for immune system diseases than women who have not had this surgery.

Similarly, the concern that breast implants increase the risk of breast cancer recurrence or formation of new cancers is not supported by current evidence.

Radiation therapy

For women who need radiation after breast-conserving surgery, newer techniques such as hypofractionated radiation or accelerated partial breast irradiation may be as effective while offering a more convenient way to receive it (as opposed to the standard daily radiation treatments that take several weeks to complete). These techniques are described in more detail in the section, "How is breast cancer treated?"

Large studies are being done to determine if these techniques are as effective as standard radiation in helping prevent cancer recurrences.

New chemotherapy drugs

Advanced breast cancers are often hard to treat, so researchers are always looking for newer drugs.

A drug class has been developed that targets cancers caused by BRCA mutations. This class of drugs is called PARP inhibitors and they have shown promise in clinical trials treating breast, ovarian, and prostate cancers that had spread and were resistant to other treatments. Further studies are underway to see if this drug can help patients without BRCA mutations.

Targeted therapies

Targeted therapies are a group of newer drugs that specifically take advantage of gene changes in cells that cause cancer.

Drugs that target HER2: There are 2 drugs approved for use that target excess HER2 protein, trastuzumab (Herceptin) and lapatinib (Tykerb). Studies continue to see which of these is best for treating early breast cancer. Other drugs that target the HER2 protein are being tested in clinical trials, including TDM-1, pertuzumab and neratinib. Researchers are also looking at using a vaccine to target the HER2 protein.

Anti-angiogenesis drugs: In order for cancers to grow, blood vessels must develop to nourish the cancer cells. This process is called *angiogenesis*. Looking at angiogenesis in breast cancer specimens can help predict prognosis. Some studies have found that breast cancers surrounded by many new, small blood vessels are likely to be more aggressive. More research is needed to confirm this.

Bevacizumab (Avastin) is an example of anti-angiogenesis drug. Although the value of bevacizumab for breast cancer is currently uncertain, clinical trials are currently testing several other anti-angiogenesis drugs.

Other new drugs are also being developed that may be useful in preventing new blood vessels from forming. Several of these drugs are now being tested in clinical trials.

Drugs that target EGFR: The epidermal growth factor receptor (EGFR) is another protein found in high amounts on the surfaces of some cancer cells. Some drugs that target EGFR, such as cetuximab (Erbitux[®]) and erlotinib (Tarceva[®]), are already used to treat other types of cancers, while other anti-EGFR drugs are still considered experimental. Studies are now under way to see if these drugs might be effective against breast cancers.

Other targeted drugs: Everolimus (Afinitor[®]) is a new type of targeted therapy drug that was recently approved to treat kidney cancer. In one study, letrozole plus everolimus worked better than letrozole alone in shrinking breast tumors before surgery. More studies using this drug are planned.

Many other potential targets for new breast cancer drugs have been identified in recent years. Drugs based on these targets are now being studied, but most are still in the early stages of clinical trials.

Bisphosphonates

Bisphosphonates are drugs that are used to help strengthen and reduce the risk of fractures in bones that have been weakened by metastatic breast cancer. Examples include pamidronate (Aredia) and zoledronic acid (Zometa).

Some studies have suggested that zoledronic acid may help other systemic therapies, like hormone treatment and chemo) work better. In one study, the women getting zolendric acid with chemo had their tumors shrink more than the women treated with chemo alone. In other studies, giving zoledronic acid reduced the risk of the cancer coming back. More studies are needed to determine if bisphosphonates should become part of standard therapy for early-stage breast cancer.

Vitamin D

A recent study found that women with early-stage breast cancer who were vitamin D deficient were more likely to have their cancer recur in a distant part of the body and had a poorer outlook. More research is needed to confirm this finding, and it is not yet clear if taking vitamin D supplements would be helpful. Still, you may want to talk to your doctor about testing your vitamin D level to see if it is in the healthy range.

Denosumab

When cancer spreads to the bone, it causes increased levels of a substance called RANKL, which is important in bone metabolism. Higher levels stimulate cells called

osteoclasts to destroy bone. A newer drug called *denosumab* inhibits (acts against) RANKL and can help protect bones. In early studies it seems to help even after bisphosphanates stop working. More studies are ongoing.

Additional resources

More information from your American Cancer Society

The following related information may also be helpful to you. These materials may be ordered from our toll-free number, 1-800- 227-2345.

- After Diagnosis: A Guide for Patients and Families (also available in Spanish)

- Bone Metastasis

- Breast Cancer Dictionary (also available in Spanish)

- Breast Cancer Early Detection (also available in Spanish)

- Breast Prostheses and Hair Loss Accessories List

- Breast Reconstruction After Mastectomy (also available in Spanish)

- Chemo brain

- Clinical Trials: What You Need to Know

- DES Exposure: Questions and Answers

- Exercises After Breast Surgery (also available in Spanish)

- Fatigue in People with Cancer

- Genetic Testing: What You Need to Know

- Inflammatory Breast Cancer

- Is Abortion Linked to Breast Cancer?

- Living With Uncertainty: The Fear of Cancer Recurrence

- Lymphedema: What Every Woman With Breast Cancer Should Know

- Mammograms and Other Breast Imaging Procedures

- Medicines to Reduce Breast Cancer Risk

- Non-cancerous Breast Conditions (also available in Spanish)

- Pregnancy and Breast Cancer

- Sexuality for the Woman with Cancer (also available in Spanish)

- Talking with Your Doctor (also available in Spanish)

- Understanding Chemotherapy (also available in Spanish)

- Understanding Radiation Therapy (also available in Spanish)

- When Your Cancer Comes Back: Cancer Recurrence

Books

The following books are available from the American Cancer Society. Call us at 1-800-227-2345 to ask about costs or to place your order.

Breast Cancer Clear and Simple

Caregiving: A Step-By-Step Resource for Caring for the Person with Cancer at Home

Couples Confronting Cancer

Lymphedema:Understanding andManaging Lymphedema After Cancer Treatment

National organizations and Web sites*

In addition to the American Cancer Society, other sources of patient information and support include:

National Breast Cancer Coalition
Toll-free number: 1-800-622-2838
Web site: www.stopbreastcancer.org

National Cancer Institute
Toll-free number: 1-800-4-CANCER (1-800-422-6237)
Web site: www.cancer.gov

Susan G. Komen for the Cure
Toll-free number: 1-877-465-6636
Web site: www.komen.org

Breast Cancer Network of Strength (formerly Y-Me National Breast Cancer Organization)
Toll-free number: 1-800-221-2141, 1-800-986-9505 (Spanish)
Web site: www.networkofstrength.org

Centers for Disease Control and Prevention (CDC)
Toll-free number: 1-800-232-4636 (1-800-CDC INFO)
Web site: www.cdc.gov

*Inclusion on this list does not imply endorsement by the American Cancer Society.

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Breast Cancer's Many Drivers

ScienceDaily (June 20, 2012) — Breast cancer is not a single disease, but a collection of diseases with dozens of different mutations that crop up with varying frequency across different breast cancer subtypes. Deeper exploration of the genetic changes that drive breast cancer is revealing new complexity in the leading cause of cancer death in women worldwide.
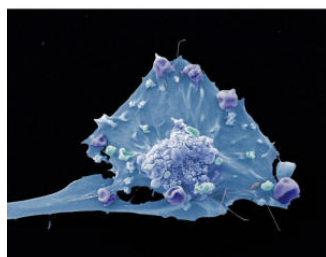
In one of the largest breast cancer sequencing efforts to date, scientists from the Broad Institute, the National Institute of Genomic Medicine in Mexico City, Beth Israel Deaconess Medical Center, and Dana-Farber Cancer Institute have discovered surprising alterations in genes that were not previously associated with breast cancer. They report their results in the June 21 issue of *Nature,* which is publishing a series of papers characterizing the genomic landscape of breast cancer.

One of the team's new findings, a recurrent fusion of the genes *MAGI3* and *AKT3* in what is known as a translocation event, was observed in tumors from a rare but aggressive form of breast cancer known as triple-negative breast cancer. This cancer does not respond to conventional hormone therapy because its tumors lack three receptors that fuel most breast cancers: estrogen receptors, progesterone receptors, and human epidermal growth factor receptor 2 (known as HER2). But the biological pathway that is affected by the *MAGI3-AKT3* reshuffling is already the target of experimental drugs.

The other new alteration reported by the team occurred in two transcription factor genes. Recurrent mutations were detected in the gene *CBFB* and deletions of its partner *RUNX1.* Cancer-causing rearrangements of these two genes are common in blood cancers, such as acute myeloid leukemia, but their discovery in breast cancer marks the first time they have been seen in a solid cancer.

"These genes wouldn't top the list of genes you think would be mutated in breast cancer," said Alfredo Hidalgo Miranda, co-senior author of the paper and head of the cancer genomics laboratory at the National Institute of Genomic Medicine, known by its Spanish acronym INMEGEN. "That's exactly the point of doing this type of analysis. It gives you the opportunity to find those genes that you never thought would be involved in the breast cancer process."

The scientists studied two kinds of samples. They sequenced the whole exomes -- the tiny fraction of the genome that encodes proteins -- of 103 breast cancer tumors and DNA from

normal tissue from patients in Mexico and Vietnam. They also sequenced the entire genomes of 22 breast cancer tumors and matched normal tissue.

Their analysis confirmed the presence of previously known mutations, but it also turned up the unsuspected alterations.

"One of the lessons here is the real diversity of mutations in breast cancer. I think it's clear there are going to be roughly 50 or so different mutated genes in breast cancer," said Matthew Meyerson, co-senior author of the paper, Broad senior associate member, and professor of pathology at Dana-Farber Cancer Institute and Harvard Medical School. "There's a big diversity of driver genes in cancer. We don't understand what all of them are, but larger data sets will enable us to identify them."

The mutations in *CBFB* and *RUNX1* point to the importance of understanding cell differentiation -- how cells become specialized -- and transcription factors that regulate that process of cell differentiation in epithelial tissue, which lines the inner and outer surfaces of the body. Further studies are needed to unravel that relationship, the authors concluded.

For the current study, inspecting the novel fusion gene *MAGI1-AKT3* more closely showed not only that the translocation can transform normal cells into cancer cells, but also that the protein produced by the gene is insensitive to certain drugs now in clinical trials, yet sensitive to others.

In general, fusion genes are created within the same chromosome or across different chromosomes when parts of one gene join parts of another to become a novel gene that wouldn't normally exist. Like the *CBFB* and *RUNX1* mutations, translocations are also more common in blood cancers but until now have rarely been detected in solid tumors, especially breast cancer.

This particular *MAGI1-AKT3* fusion gene produces a fusion protein that acts in the PI 3-kinase pathway as an oncogene, or a gene that drives cancer, revealing a new target for potential therapy. The kinase pathway controls a multitude of cellular functions. When a gene is mutated in this pathway, the result is uncontrolled cell growth, a hallmark of cancer.

Other gene mutations in this pathway are well-known, but *MAGI1-AKT3* is a first.

"This is the first translocation event resulting in an oncogenic fusion protein that has been identified in this pathway," said Alex Toker, a professor in the department of pathology at Beth Israel Deaconess and Harvard Medical School. "That's important because this is one of the most frequently mutated pathways in human cancer, especially in women's cancers such as breast, ovarian, and endometrial cancer."

The most frequently mutated pathway is also the most studied and, from a pharmaceutical perspective, among the most "druggable."

In laboratory dishes, tests confirmed that the novel structure of proteins encoded by the fusion gene provided no place for some drugs to bind but offered targets for other drugs.

"There are many additional studies that need to be performed using mouse models of disease that would recapitulate the expression of this protein in the mammary gland, in addition to the

mechanism by which this protein promotes the effects associated with malignancy," Toker said. "These are all experiments that are under way."

Once the mechanism at work in triple-negative breast cancer is understood through animal models, the next step would be to test chemical compounds to see how effective they might be at targeting cells that harbor this fusion gene's protein.

Beyond these scientific findings, the study also represents a closer look at the Latino population, thanks to the collaboration between the Broad and INMEGEN forged through the Slim Initiative in Genomic Medicine.

"The Slim Initiative in Genomic Medicine aims to support the discovery of the genetic basis of diseases such as type 2 diabetes mellitus and several types of cancer which have a profound public health impact in Mexico and Latin America," said Roberto Tapia-Conyer, director general of the Carlos Slim Health Institute. "This novel bi-national scientific collaboration is contributing to put the Latin American genome on the map of the second generation worldwide genome studies."

INMEGEN scientists had previously built a large breast cancer study and then scientists at both the Broad and INMEGEN exchanged clinical, biological, and computational information.

"From the Mexican point of view, you can say the Latino population has not been extensively characterized using genomic methods," Hidalgo Miranda said. "This is a significant contribution to the knowledge of the architecture of breast tumors in this particular population."

The study represented a first opportunity to study the genetic basis of breast cancer in Mexico. Larger studies will be required to determine whether differences in the spectrum of mutations exist between different populations, but this was an important first step toward that goal.

Contributors to the work also include, from the Broad and its Harvard-affiliated hospitals: Shantanu Banerji (co-first author), Kristian Cibulskis (co-first author), Kristin K. Brown (co-first author), Scott L. Carter, Abbie M. Frederick, Michael S. Lawrence, Andrey Y. Sivachenko, Carrie Sougnez, Lihua Zou, Maria L. Cortes, Shouyong Peng, Kristin G. Ardlie, Daniel Auclair, Fujiko Duke, Joshua Francis, Joonil Jung, Robert C. Onofrio, Melissa Parkin, Nam H. Pho, Alex. H. Ramos, Steven E. Schumacher, Nicolas Stransky, Kristin M. Thompson, Jose Baselga, Rameen Beroukhim, Kornelia Polyak, Dennis C. Sgroi, Andrea L. Richardson, Eric S. Lander, Stacey B. Gabriel, Levi A. Garraway, Todd R. Golub, and Gad Getz (co-senior author). From Mexico: Claudia Rangel-Escareno (co-first author), Juan C. Fernandez-Lopez, Veronica Bautista-Pina, Antonio Maffuz-Aziz, Valeria Quintanar-Jurado, Rosa Rebollar-Vega, Sergio Rodriguez-Cuevas, Sandra L. Romero-Cordoba, Laura Uribe-Figueroa, Gerardo Jimenez-Sanchez, and Jorge Melendez-Zajgla.

Broccoli - more evidence that spicing up broccoli boosts its cancer-fighting power

Enhancing sulforaphane absorption and excretion in healthy men through the combined consumption of fresh broccoli sprouts and a glucoraphanin-rich powder

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Abstract

Sulforaphane (SF) is a chemopreventive isothiocyanate (ITC) derived from glucoraphanin (GRP) hydrolysis by myrosinase, a thioglucoside present in broccoli. The ability of broccoli powders sold as supplements to provide dietary SF is often of concern as many supplements contain GRP, but lack myrosinase. In a previous study, biomarkers of SF bioavailability from a powder rich in GRP, but lacking myrosinase, were enhanced by co-consumption of a myrosinase-containing air-dried broccoli sprout powder. Here, we studied the absorption of SF from the GRP-rich powder used in the previous study, but in combination with fresh broccoli sprouts, which are commercially available and more applicable to the human diet than air-dried sprout powder. A total of four participants each consumed four meals (separated by 1 week) consisting of dry cereal and yogurt with sprouts equivalent to 70 μmol SF, GRP powder equivalent to 120 μmol SF, both or neither. Metabolites of SF were analysed in blood and urine. The 24 h urinary SF-*N*-acetylcysteine recovery was 65, 60 and 24 % of the dose ingested from combination, broccoli sprout and GRP powder meals, respectively. In urine and plasma, ITC appearance was delayed following the GRP powder meal compared with the sprout and combination meals. Compared with the GRP powder or sprouts alone, combining broccoli sprouts with the GRP powder synergistically enhanced the early appearance of SF, offering insight into the combination of foods for improved health benefits of foods that reduce the risk for cancer.

Key words: Broccoli: Cancer: Glucoraphanin: Sulforaphane

Sulforaphane (SF), found in broccoli as its inactive precursor glucoraphanin (GRP), is considered to be responsible for the reduction of cancer risk that is associated with broccoli consumption. Upon crushing or chewing of fresh broccoli or broccoli sprouts, GRP is hydrolysed to SF by the plant thiohydrolase myrosinase. In instances of myrosinase inactivation, such as overcooking of broccoli, GRP can be hydrolysed to SF by microflora present in the lower gut[1,2]. However, GRP hydrolysis by microflora of the lower gut is far less efficient than hydrolysis by endogenous broccoli myrosinase[3–6].

SF protects against the incidence and progression of cancer via several mechanisms including inhibiting phase I cytochrome P450 enzymes, inducing cell-cycle arrest and apoptosis, reducing inflammation, and perhaps most well-characterised, modulating the nuclear factor-erythroid-2-related factor 2/Kelch-like ECH-associated protein 1 pathway[7]. In the body, SF is metabolised by the mercapturic acid pathway and excreted in the urine, mostly as SF-*N*-acetylcysteine (SF-NAC)[8,9]. The fate of non-hydrolysed GRP is less well

understood. A recent study has reported that low amounts of intact GRP were recovered in the urine of human subjects after consumption of a GRP-rich beverage, but not after consumption of an SF-rich beverage[9]. Another study has reported that low amounts of intact GRP were recovered in the urine, but not in the faeces of rats that were fed purified GRP[10].

Several small clinical studies have examined the absorption and excretion of SF in human subjects. When urinary excretion of isothiocyanates (ITC) was measured following ingestion of fully cooked or fresh/lightly cooked broccoli, urinary ITC metabolites were approximately three times greater from fresh/lightly cooked broccoli than from fully cooked broccoli where myrosinase had been heat-inactivated[3,4]. Similar studies have evaluated the appearance of total ITC in the urine following ingestion of broccoli sprouts that had been either completely hydrolysed to ITC using exogenous myrosinase or contained only GRP where the myrosinase had been destroyed by boiling[5,9]. It has been found that ITC excretion was much greater after consumption of the preformed ITC compared

with the GRP preparations[5,9]. The results of these studies suggest that the conversion of GRP to SF and subsequent ITC bioavailability is dependent on active myrosinase.

In a previous study, a commercially available GRP powder devoid of myrosinase, typical of many dietary GRP supplements on the market, was examined for its potential to deliver bioactive SF to human subjects alone or in combination with the air-dried broccoli sprout powder, which served as an exogenous food source of myrosinase[6]. The results showed that the combination improved the absorption of SF, and thus opened the door to the potential for enhanced cancer risk reduction not only from GRP supplements, but also from specifically designed foods or food combinations[6].

Due to commercial availability and consumer preferences, intact fresh broccoli sprouts are more likely to be ingested by humans than the air-dried broccoli sprout powder used in our previous study. However, fresh broccoli sprouts may present additional variables such as matrix effects or product variability that were not present when examining the air-dried broccoli sprout powder. Therefore, the present study examined the same commercially available GRP powder used in our previous study, but here, intact fresh broccoli sprouts were used as the exogenous food source of myrosinase. The present study also expanded the number of blood samples collected to better capture the differences in SF appearance in plasma from the test meals. The study sought to determine whether the fresh broccoli sprouts would enhance GRP conversion and ITC absorption from the GRP powder.

Methods

Fresh broccoli sprouts were donated by Tiny Greens Organic Farm (Urbana, IL, USA). Broccoli powder was a gift from Caudill Seed, Inc. (Louisville, KY, USA).

Human subject study population

A total of four healthy men, aged 18–30 years, were recruited by fliers at the University of Illinois at Urbana-Champaign. Before participating in the study, each subject completed baseline questionnaires regarding dietary supplement, tobacco and other drug use. The present study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the University of Illinois Institutional Review Board. Written informed consent was obtained from all subjects. The study took place between 31 January and 25 February 2009.

Study design, meal administration and sample collection

Subjects were randomly assigned to a four-by-four cross-over design. They were given a list of foods known to contain glucosinolates and asked to avoid these foods for 3 d before and throughout the entire duration of the study. Subjects were also requested to avoid the use of dietary supplements and to limit alcohol consumption to no more than two alcoholic beverages per d during the study. Experimental meals were given each Tuesday for 4 weeks resulting in a 6 d washout period between meals; the half-life for SF has been reported as approximately 2 h[11,12]. On the morning of each trial, subjects were instructed to ingest a meal according to the cross-over design. In the case of sprout-containing meals, subjects were also instructed to chew the sprouts thoroughly. Meals included 5-d-old intact fresh broccoli sprouts of the calabrese variety (approximately 42 g) or GRP powder (2 g) in an amount that produced 70 or 120 μmol SF, respectively, determined by bench hydrolysis. The combination meal contained both intact fresh broccoli sprouts (approximately 42 g) and GRP powder (2 g). The GRP powder was a proprietary dry, defatted broccoli seed powder preparation that did not contain myrosinase. Experimental meals were accompanied by one cup (53 g) of dry cereal (Go Lean Crunch; Kashi Company, La Jolla, CA, USA) and half cup (113·5 g) of French vanilla fat-free yogurt (Stonyfield Farm, Londonderry, NH, USA) to serve as a vehicle and control meal. Thus, the control meal included cereal and yogurt only. Blood (8 ml) was drawn into EDTA vacutainer tubes (Becton, Dickinson & Company, Franklin Lakes, NJ, USA) immediately before ingestion of each meal (0 h), and at 0·5, 1·0, 1·5, 3·0 and 24 h following the meal. Plasma was immediately prepared by centrifugation and stored at −80°C until analysed. Urine samples were collected at baseline (0 h), 0–6, 6–12 and 12–24 h after meal consumption. All urine voided during these time intervals was collected. The volumes were recorded and used to calculate total μmol of SF-NAC excreted. Baseline urine samples were kept on ice and ascorbic acid (Fisher Scientific, Pittsburgh, PA, USA) was added to the urine samples at 1 g/l urine no later than 1 h following collection. All other urine samples were collected into 500 ml bottles containing 0·5 g ascorbic acid. Subjects were instructed to store urine samples in a provided cooler and to return them the following morning when the 24 h blood samples were collected. Urine samples were then stored at −80°C until analysed.

Sulforaphane analysis

In triplicate, GRP powder (50 mg) was added to 1·6 ml distilled water containing 0·8 U white mustard myrosinase (Sigma Chemical, St Louis, MO, USA), vortexed and left to hydrolyse in the dark for 24 h. (One unit of myrosinase produces 1·0 μmol glucose/min from sinigrin at pH 6·0 and 25°C.) The mixture was then centrifuged for 5 min at 14 000 $\boldsymbol{g}$ and filtered through a 0·45 μm nylon filter. The supernatant was diluted 5-fold with distilled H_2O and an internal standard of benzyl ITC (Sigma Chemical) was added. The analysis of the GRP powder was also conducted in the absence of added myrosinase to confirm the necessity of myrosinase in the conversion of GRP to SF. Fresh broccoli sprouts were obtained the day before each trial meal and analysed for SF production upon hydrolysis using a modification of a previously reported method[13]. In triplicate, 0·25 g fresh broccoli sprouts were heated at 90°C for 5 min in a glass vial containing 2 ml distilled water. Following heating, samples were cooled on ice,

homogenised and 0·5 U white mustard myrosinase were added. Samples were vortexed and left to hydrolyse at room temperature for 2 h. The samples were then centrifuged for 5 min at 14 000 *g*. The supernatant was filtered through a 0·45 µm nylon filter and diluted 4-fold with distilled water. An internal standard of benzyl ITC was added. ITC were extracted into dichloromethane for analysis by GC, as described previously[6].

Plasma total isothiocyanate analysis

Blood samples were collected in EDTA-coated tubes and centrifuged at 1000 *g* for 30 min. Plasma was collected and analysed as described previously[6]. This method provides a single total measurement for SF, other ITC and metabolites[14,15].

Urinary sulforaphane-N-acetylcysteine analysis

Urine samples were analysed as described previously[6]. Briefly, the filtered urine (50 µl) was analysed by HPLC using a Hypersil C18 ODS column (10 µm, 250 × 4·6 mm; Phenomenex, Torrance, CA, USA) and detected at 254 nm using a Waters HPLC system. A gradient solvent system with a flow rate of 1 ml/min consisted of a starting solvent system of 5% aqueous acetonitrile (Fisher Scientific) and 95% water. Acetonitrile was increased linearly to 20% over 3 min, held 4 min, then increased to 100% over 2 min and held 13 min to rinse the column. Both solvents contained 1·0% acetic acid (Fisher Scientific). A standard was generated in control urine using SF-NAC synthesised as described previously[16].

Statistical analysis

Data were evaluated using the GLIMMIX procedure of SAS Statistical software (version 9.1; SAS Institute, Cary, NC, USA). Levels of SF metabolites in urine and blood were tested for interactions of treatment and time. Differences were separated using the SLICEDIFF option. Values were considered different at $P < 0.05$.

Results

Sulforaphane content of hydrolysed broccoli sprouts and glucoraphanin powder

Upon incubation in water at room temperature for 24 h with the addition of 0·8 U myrosinase, GRP powder produced 61·7 (SE 2·1) µmol SF/g powder. No SF was produced in the absence of added myrosinase. Fresh broccoli sprouts produced 1·69 (SE 0·12) µmol SF/g fresh weight.

Plasma total isothiocyanates

Plasma ITC were elevated compared with baseline at 0·5 h in both the sprout and combination meals (Table 1). The combination meal reached peak plasma concentration (2·86 (SE 0·33) µmol/l) 1·5 h after ingestion. The sprout meal peaked at 3 h (1·53 (SE 0·22) µmol/l), but this value was not different from the value at 1·5 h (1·43 (SE 0·21) µmol/l). The GRP powder meal showed slightly elevated plasma concentration levels 3 h post-consumption (0·37 (SE 0·25) µmol/l). However, values following the GRP powder meal were not different from the control meal or baseline measurements at any of the time points measured. All values returned to baseline values by 24 h.

Sulforaphane-N-acetylcysteine in the urine

The amount of SF-NAC excreted in the urine over 24 h following ingestion of each meal is shown in Fig. 1. After ingestion of fresh broccoli sprouts in combination with GRP powder, individuals excreted a mean of 123·8 (SE 8·8) µmol SF-NAC over 24 h post-ingestion, 65% of the dose ingested. After ingestion of broccoli sprouts alone, a mean of 42·0 (SE 11·8) µmol SF-NAC was excreted, 60% of the ingested dose. However, after ingesting GRP powder alone, a mean of only 29·2 (SE 5·0) µmol SF-NAC was excreted, 24% of the dose ingested.

Urine collection was separated into discrete intervals for evaluation of SF-NAC excretion: urine was collected for the first 6 h after meal ingestion, from 6 to 12 h and from 12 to 24 h post-ingestion. Significant differences were observed between the dietary groups. Considerable levels of SF-NAC were excreted during the first 6 h from individuals who received the combination meal or the broccoli sprout meal (61 and 62% of the total SF-NAC that was excreted during the entire 24 h urine collection, respectively), but less than 22% of the total 24 h SF-NAC was excreted during this first 6 h period from those receiving the GRP powder meal alone. In contrast, less than 10% of the total 24 h SF-NAC recovered from the combination or sprout meal was excreted

Table 1. Total isothiocyanate (ITC) in plasma following test meal consumption

(Mean values with their standard errors for four subjects per group)

Total ITC/l (µmol)	0 h		0.5 h		1 h		1.5 h		3 h		24 h	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Control	0.22[a,A]	0.09	0.18[a,b,A]	0.11	0.24[a,A]	0.06	0.16[a,A]	0.13	0.05[a,A]	0.03	0.05[a,A]	0.04
GRP powder	0.09[a,A]	0.07	0.11[a,A]	0.07	0.07[a,A]	0.03	0.12[a,A]	0.11	0.37[a,A]	0.25	0.16[a,A]	0.10
Fresh sprout	0.13[a,A]	0.12	0.46[b,A]	0.11	0.97[b,B]	0.15	1.43[b,C]	0.21	1.53[b,C]	0.22	0.19[a,A]	0.07
Combination	0.10[a,A]	0.07	1.26[c,B]	0.22	2.14[c,C]	0.15	2.86[c,D]	0.33	2.57[c,D]	0.38	0.30[a,A]	0.07

GRP, glucoraphanin.

[a,b,c] Mean values within a column (between-meal values) with unlike superscript letters were significantly different ($P < 0.05$).

[A,B,C,D] Mean values within a row (within-meal values) with unlike superscript letters were significantly different ($P < 0.05$).
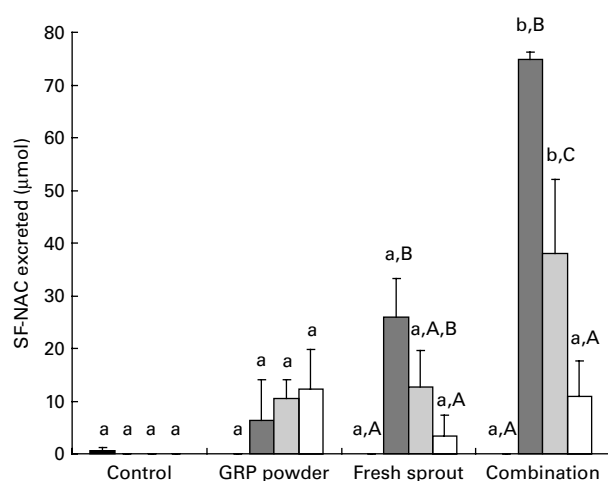
Fig. 1. Urinary sulforaphane-*N*-acetylcysteine (SF-NAC) excretion after consumption of four different meals: control; glucoraphanin (GRP) powder; fresh broccoli sprout; combination. Baseline (■), 0–6 h (■), 6–12 h (□) and 12–24 h (□) urine collection post-consumption. Values are means, with their standard errors represented by vertical bars for four subjects per group. [a,b] Mean values with unlike letters were significantly different between-meal ($P<0.05$). [A,B,C] Mean values with unlike letters were significantly different within-meal ($P<0.05$).

during the 12–24 h period, whereas 42 % of the total 24 h SF-NAC recovered following the GRP powder meal was excreted during this later time period.

Discussion

The main findings of the present study were that combining fresh broccoli sprouts with the GRP powder (1) increased the appearance of SF metabolites in plasma and urine and (2) removed the delay of metabolite appearance observed after the GRP powder, shifting the absorption/elimination pattern to the one similar to that seen after the consumption of fresh broccoli sprouts alone. This is the first study to determine whether combining two commercially available broccoli products, one containing and the other lacking myrosinase, would enhance SF availability from GRP. The present study could be extrapolated to hypothesise that combining fresh broccoli sprouts with well-cooked broccoli, where myrosinase is inactive, would also enhance SF availability. Additionally, it could be hypothesised that other sources of myrosinase, such as mustard, horseradish, cabbage, Brussels sprouts and watercress, would also enhance the conversion of GRP to SF.

The present study measured urinary SF-NAC excretion and plasma total ITC levels. The measurement of SF metabolites after consumption of broccoli, broccoli sprouts and other broccoli-related preparations has been a useful tool for assessing human exposure to SF, a compound associated with a reduced risk of cancer[1,3–6,9,17,18]. SF metabolites in plasma reflect the amount of SF that tissues are being exposed to and are therefore important biomarkers of exposure to this cancer-preventive agent. SF metabolites in the urine reflect the absorption, metabolism and excretion of an ingested dose[5]. The major metabolite of SF appearing in the urine,

SF-NAC, is often used as a marker of bioavailability, although it is not the only metabolite present in the urine[8,9].

Only 24 % of the GRP dose from the GRP powder was recovered as SF-NAC in the urine, making it a poor source of dietary SF compared with fresh broccoli sprouts. This value is comparable with the reported recovery following ingestion of well-cooked sprouts or well-cooked mature broccoli, both of which also lacked myrosinase[3,5,18]. Urinary values of SF-NAC after the GRP powder meal displayed a non-significant trend of increasing excretion over 24 h, suggestive of delayed absorption. The delayed absorption and low SF recovery was probably due to the lack of myrosinase in the powder and the resulting hydrolysis of GRP by microflora after the transit of GRP to the lower gut[1,2,18,19]. Plasma total ITC was not altered in response to the GRP powder, but there was a slight non-significant elevation at 3 h, also suggestive of delayed ITC absorption with low availability. It could be questioned whether the maximum plasma ITC level was further delayed rather than absent following ingestion of the GRP powder, and thus was not measured in the present study. Indeed, a slight, but non-significant peak 6 h post-consumption was observed in a study of well-cooked broccoli[3]. However, urinary recovery of SF-NAC was low not only for the first 6 h of the present study, but for the entire 24 h period following consumption of the GRP powder meal, confirming the absence of any significant elevation in plasma ITC levels. The low levels of SF metabolites detected in plasma and urine after consumption of the GRP powder may indicate lower anti-cancer potential for this product and other similar dietary supplements. For instance, it has been reported that similar GRP products lacking myrosinase induced detoxification enzymes in the colon, but not in the liver of rats, whereas unheated broccoli florets with functional myrosinase induced activity in both the colon and the liver[20].

Interestingly, data from the combination meal identified possible synergy among the fresh sprouts and GRP powder at early time points for SF and its metabolite appearance in plasma and urine. This indicates that GRP, not only from the broccoli sprouts, but also from the GRP powder, was hydrolysed by endogenous myrosinase from the broccoli sprouts. Additionally, excretion of SF-NAC following the combination meal was earlier than from the GRP powder alone and more similar to the excretion pattern following the consumption of broccoli sprouts alone, indicating that the fresh sprouts not only supported the hydrolysis of the GRP powder, but also caused it to occur earlier, resulting in earlier and more complete SF absorption. The trend for greater levels of SF-NAC to be excreted early (during the first 12 h following meal consumption) from the combination and sprout meals is consistent with metabolism occurring in the upper gastrointestinal tract in the presence of dietary myrosinase. A similar trend was observed in plasma where in both sprout and combination meals, plasma ITC levels were elevated by 0·5 h, and to a much higher level in the combination meal. Higher levels of SF metabolites in plasma and urine may indicate a greater reduction of cancer risk from consumption of this food combination.

Recovery of preformed ITC or ground, air-dried broccoli sprouts has been reported to be between 75 and 90% of ingested doses[5,6,21]. This recovery decreased when a plant matrix was introduced, as is evidenced by several published papers, as well as the present paper where intact, but thoroughly chewed fresh sprouts resulted in a 60% recovery of the dose[3,5,21]. Interestingly though, comparing an equimolar dose of SF from fresh sprouts (used here) with air-dried sprouts[6] when combined with the GRP powder, an improved 24 h urinary recovery (65 v. 50% of the ingested dose, respectively) and an elevated peak plasma ITC level (C_{max} 2·9 v. 2·1 μmol total ITC/l, respectively) was observed in the combination using fresh intact broccoli sprouts. Based on this evidence, we conclude that fresh broccoli sprouts aided the conversion of GRP to SF from the GRP powder to a greater extent than air-dried broccoli sprouts. More research with larger study populations is needed.

One limitation of the present study is its small sample size. However, most human studies focusing on the bioavailability of SF have used similar small population sizes[3,5,6,11]. The intent of the present study was to provide direction as a pilot study. Future large-scale work is needed.

Conclusion

GRP powder that lacked myrosinase was a poor dietary source of SF compared with broccoli sprouts. Fresh intact broccoli sprouts were able to synergistically enhance the hydrolysis of GRP from the GRP powder, perhaps more efficiently than ground, air-dried broccoli sprouts. Because efficacy is related to plasma levels, the elevation seen in plasma levels probably translates to a greater potential for cancer risk reduction. These findings provide important insights into the protective health benefit of broccoli products and preparations and can be used to develop foods with enhanced anti-cancer properties.

Acknowledgements

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Cells lining milk ducts hold key to spread of ductal carcinoma in situ

Kornelia Polyak, MD, PhD

When a form of cancer that begins in the milk ducts of the breast invades neighboring tissue to spread to other parts of the body, the cause lies not in the tumor cells themselves but in a group of abnormal surrounding cells that cause the walls of the duct to deteriorate like a rusty pipe, according to a new study led by Dana-Farber Cancer Institute researchers.

The discovery, reported in the May 6 issue of *Cancer Cell*, may lead to screening tests to determine whether the disease — known as ductal carcinoma in situ, or DCIS — is likely to spread beyond the ducts, based on genetic abnormalities in cells in the ducts' lining. And it sets the stage for treatments that, by targeting these abnormalities, shore up the duct walls and keep the cancer contained.

"Women whose DCIS has invaded the ducts are known to have a greater chance of metastasis, or spreading disease. But it hasn't been clear what causes the transition from a localized cancer to invasive disease," according to the study's senior author, **Kornelia Polyak, MD, PhD**, of Dana-Farber. "This study demonstrates that in DCIS of the breast, and potentially in other cancers that originate in duct tissues, the answer may lie in the tumor's microenvironment — the cells and tissue that surround the cancer."

DCIS is expected to be diagnosed in nearly 53,000 women in the United States this year. When detected and surgically removed before it has a chance to spread, the disease is nearly always curable. It isn't known how many of these cancers would become invasive breast cancer if they weren't treated, but studies suggest that most of them eventually would.

Researchers initially thought that DCIS might become invasive as a result of genetic changes in the cancer cells. When they surveyed gene activity in immobile DCIS cells and in those that had spread, however, they found no significant differences. That led them to consider the cell's microenvironment.

Polyak and her colleagues focused on myoepithelial cells, which form part of the lining of the milk ducts and are involved in breast development, as well as impeding the growth and invasiveness of some cancer cells. To study what role, if any, these cells play in DCIS, the researchers worked with a specially engineered line of cells known as MCFDCIS.

When injected in laboratory animals, the MCFDCIS cells formed DCIS-like tissue that developed into invasive tumors, providing a good model of what happens in human disease. When researchers injected both MCFDCIS and myoepithelial cells into the mice, DCIS tumors arose, but they were confined to the ducts. When they injected MCFDCIS cells and fibroblasts

— cells found in milk ducts and other connective tissue — the resulting DCIS tumors broke into the walls of the ducts.

"These findings made it clear that fibroblasts promote tumor growth and invasion, and normal myoepithelial cells suppress it," Polyak remarks. But when certain genes in the myoepithelial layer become under- or overactive, the layer breaks down and disappears, enabling tumor cells to escape.

To identify which genes are affected and what causes their activity level to change, Polyak's team surveyed the activity of thousands of genes in myoepithelial and DCIS cells using advanced SAGE (Serial analysis of gene expression) technology. When DCIS tumors trespass into the lining of the ducts, the activity level of several myoepthelial cell genes is abnormal — specifically the TGF Beta, Hedgehog, and p63 genes as well as genes that help myoepithelial cells stick to "basement" cells on the ducts' outer layer. The effect is a cacaphony of erratic signals and haywire activity that prevents myoepithelial cells from fully maturing and forming an effective barrier to DCIS.

"We found a constant, complex interplay of signals among these genes, both within myoepithelial cells themselves, and between myoepithelial cells and their neighbors," Polyak says. "The presence of DCIS causes the pattern of signals to change significantly, upsetting the normal development of myoepithelial cells. The myoepithelial cells fail to fully differentiate" — act as true 'gatekeepers' for DCIS — "leading to the disappearance of the myoepithelial layer and the beginning of tumor invasion."

The discovery suggests that by scanning myoepithelial tissue for abnormalities in these key genes, doctors may be able to identify which women with DCIS have the greatest risk of cancer spread, says Polyak, who is also an associate professor of medicine at Harvard Medical School. It also provides numerous targets for future drugs aimed at restoring the normal balance of signals among these genes.

"Our results highlight the importance of the microenvironment in breast tumor progression," Polyak remarks. "And they suggest that therapies that target the interactions of tumor cells with their surroundings may offer a better way of inhibiting tumor progression than those that focus on the tumor epithelial cells alone."

The study's lead author is Min Hu, PhD, of Dana-Farber. Co-authors are Jun Yao, PhD, Haiyan Chen, PhD, Erica Bauerlein, Daniel Carrasco, MD, PhD, William Hahn, MD, PhD, and Rebecca Gelman, PhD, of Dana-Farber; Stanislawa Weremowicz, PhD, and Andrea Richardson, MD, PhD, of Brigham and Women's Hospital; Danielle Carroll, PhD, of Harvard Medical School; Sheila Violette, PhD, of Biogen-Idec of Cambridge, Mass.; Tatiana Nikolskaya, PhD, and Yuri Nikolsky, PhD, of GeneGo, Inc., of St. Joseph, Mich.; Craig Allred, MD, of Washington University School of Medicine; Mina Bissell, PhD, of Lawrence Berkeley National Laboratory; and Stuart Schnitt, MD, of Beth Israel Deaconess Medical Center.

Dana-Farber Cancer Institute (www.dana-farber.org) is a principal teaching affiliate of the Harvard Medical School and is among the leading cancer research and care centers in the United States. It is a founding member of the Dana-Farber/Harvard Cancer Center (DF/HCC), designated a comprehensive cancer center by the National Cancer Institute.

Cochrane review on screening for breast cancer with mammography

Ole Olsen, Peter C Gøtzsche

In 2000, we reported that there is no reliable evidence that screening for breast cancer reduces mortality. As we discuss here, a Cochrane review has now confirmed and strengthened our previous findings. The review also shows that breast-cancer mortality is a misleading outcome measure. Finally, we use data supplemental to those in the Cochrane review to show that screening leads to more aggressive treatment.

We previously assessed the results of the seven randomised trials of screening mammography, and concluded that screening is unjustified because there is no reliable evidence that it reduces mortality.[1] We reassessed this finding in a Cochrane review[2] in which we paid close attention to the standard dimensions of methodological quality of trials: the randomisation method, baseline comparability, exclusions after randomisation, and unbiased assessment of outcome (see protocol for the Cochrane review [issue 3, 2001, Cochrane Library]). Additionally, we noted whether early introduction of screening in the control group had occurred. Details of the trial assessments are presented in our review.[2] On the basis of these assessments, we classified the quality of the available trial data into four groups: high, medium, poor, and flawed.

We found that the results confirmed and strengthened our original conclusion. No trial data were of high quality, two were of medium quality (Malmö and Canada), three were of poor quality (Two-County, Stockholm, and Göteborg), and two were flawed (New York and Edinburgh). The review provided evidence that assessment of cause of death is unreliable and biased in favour of screening. Even when endpoint committees masked to group assignment were used, uncertain causes of death were significantly more commonly ascribed to breast cancer than to other causes in the control group. The credibility of this finding is supported by another meta-analysis, which showed that radiotherapy reduces local recurrence by two-thirds.[3] Treatment of early cancers by tumourectomy and radiotherapy might increase the likelihood that deaths among screen-detected breast cancer cases will be misclassified as deaths from other causes,[3] particularly other cancers.[2] We noted that the two trials with medium-quality data failed to find an effect of screening on deaths ascribed to any cancer, including breast cancer (relative risk 1·02 [95% CI 0·95-1·10]). The estimate for the trials with poor-quality data was similar (1·00 [0·91-1·10]). Furthermore, the greater use of radiotherapy in screened women than in controls[1] is expected to increase overall mortality because of cardiovascular adverse effects.[3] These deaths were not counted as deaths related to screening in the trials we assessed.

The main outcome measure in the screening trials was breast-cancer mortality. This choice seems rational, since larger trials would be needed to show an effect on overall mortality. However, we showed that the assumption that a demonstrated effect on breast-cancer mortality can be translated into a reduction in overall mortality rests on

suppositions that are not correct.[2] The only reliable mortality estimates are therefore those for overall mortality. The relative risk of overall mortality was 1·00 (0·96-1·05) in the two trials of highest methodological quality (figure).[2] The Swedish trialists have recently reported an updated mortality estimate for the four Swedish trials:[4] this estimate was also 1·00 (0·98-1·02) after adjustment for imbalances in age that had occurred despite attempts at randomisation.[1,2] Thus, although the trials were underpowered for all-cause mortality, the reliable evidence does not indicate any survival benefit of mass screening for breast cancer.

In our previous paper,[1] we divided the trials into two groups on the basis of methodological quality. We reported that the effect estimate for breast cancer mortality in the two best trials was significantly different from that for the five poor-quality trials, which is a sign that something is wrong. In our latest review, we therefore omitted the trials from New York and Edinburgh from the analysis of the poor-quality trials, since they are flawed.[2] However, there was still a significant difference between the two estimates for breast-cancer mortality. The two best trials failed to find an effect of screening on deaths ascribed to breast cancer (relative risk 0·97 [0·82-1·14) after 13 years, whereas the three remaining trials with poor-quality data found a marked effect (0·68 [0·58-0·78]; p=0·001 for the difference between the two effect estimates). Given the strong heterogeneity, results from the different quality groups should not be combined.

The largest effects on breast-cancer mortality were reported in trials that had long intervals between screenings (Two-County trial), that invited many women to only two or three screenings (Two-County and Stockholm trials), that started systematic screening of the control group after 3-5 years (Two-County trial, Göteborg trial, and Stockholm trial) and that had poor equipment for mammography (New York trial). This surprising situation suggests that differences in reported effects between the trials are related to the methodological quality of the trials and not to the quality of the mammograms or the screening programmes.[2]

We have also confirmed, with additional data (see www.thelancet.com), which the editors of the Cochrane Breast Cancer Group have elected to defer from publication until further editorial review has been completed, our earlier finding[1] that screening leads to more aggressive treatment, increasing the number of mastectomies by about 20% and the number of mastectomies and tumourectomies by about 30%. The greater use of surgery was not merely an initial phenomenon caused by the tumours detected at the prevalence screen, but seemed to persist. The increased mastectomy rate in the trials might be higher than in current practice, since there has been a general policy change towards fewer mastectomies. However, screening identifies some slow-growing tumours that would never have developed into cancer in the women's remaining lifetimes, as well as cell changes that are histologically cancer but biologically benign. Furthermore, carcinoma in situ does not always develop into invasive cancer, but since these early lesions are often diffuse, women are sometimes treated by bilateral mastectomy. Therefore, the increase in surgery rates could also be an underestimate, since reoperations and operations in the contralateral breast seemed not to have been included. Furthermore, "better" diagnostic methods--eg, better mammograms--could

lead to additional overtreatment because of detection of even more early or questionable lesions. Quality assurance programmes could possibly reduce the surgical activity to some degree, but the problem cannot be avoided.

Our earlier report[1] has been criticised,[5,6] especially for its emphasis on imbalances in baseline variables. However, the main reason for the ongoing controversy is probably that our opponents keep referring to the criticisms of our paper without referring to our reply.[7] Furthermore, they seem to have ignored this sentence in our paper: "Our analyses focused on age as a marker for imbalance as this was the only baseline information we had available for the Swedish trials".[1] We have not postulated that the baseline imbalances per se caused the inflated effect, but we used the imbalances as markers of poor trial methodology[7]--an approach that led us to new important information about the trials.[2] Contrary to what the critics assert,[6] the fact that that there was no age imbalance in the two best trials was confirmed in the correspondence that followed our *Lancet* paper, and we believe that all relevant criticism has now been addressed in our review.[2]

We have provided detailed evidence on the mammography screening trials, and hope that women, clinicians, and policy-makers will consider these findings carefully when they decide whether or not to attend or support screening programmes. Any hope or claim that screening mammography with more modern technologies than applied in these trials will reduce mortality without causing too much harm will have to be tested in large, well-conducted randomised trials with all-cause mortality as the primary outcome. This study was funded by the Danish Institute for Health Technology Assessment.

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Could acid in breast milk be the answer to beating cancer?

Submitted by Drew Kaplan on April 22, 2010 – 11:44 am

A substance found in breast milk can kill cancer cells, claim researchers.
For the first time, the substance – known as Hamlet – has been successfully tested on humans. Patients with bladder cancer who were treated with Hamlet managed to expel dead cancer cells through their urine after each treatment, raising hopes it could be a potential cure. In the laboratory, the substance has been found to kill 40 types of cancer cell, with the advantage that it leaves healthy cells undamaged.

The discovery, published in the science journal PloS One, has been made by researchers at the University of Gothenburg and Lund University in Sweden.

It is the latest breakthrough
involving health benefits from ingredients found in mother's milk.

Breastfeeding is already known to protect against childhood tumours.

And last week U.S. researchers revealed that lauric acid combats acne and could form the basis of a new treatment which avoids side effects linked with traditional drugs, including skin redness.

Hamlet – Human Alpha-lactalbumin Made Lethal to Tumour cells – was discovered unintentionally when researchers were investigating the antibacterial properties of breast milk.

The substance consists of a protein and a fatty acid found naturally in breast milk.

Previous experiments have not tested Hamlet in patients.

Assistant Professor Roger Karlsson, from the University of Gothenburg's department of chemistry, said he hoped Hamlet could be developed into a cancer drug.

'Laboratory experiments have shown that Hamlet kills 40 different types of cancer, and the researchers are now going on to study its effect on skin cancer, tumours in the mucous membranes and brain tumours,' he said.

'Importantly, Hamlet kills only cancer cells and does not affect healthy cells.'

Prof Karlsson said the chemical was discovered 'by chance'.

The Swedish research team extracted it from breast milk to test it on cancer patients and used injections to insert it directly into tumours.

He said: 'Although the substance was discovered in breast milk several years ago, it is only now that it has been possible to test it on humans.

'Patients with cancer of the bladder who were treated with the substance excreted dead cancer cells in their urine after each treatment, which has given rise to hopes that it can be developed into medication for cancer care in the future.'

Prof Karlsson's work is based on combining the chemical from breast milk with a fatty acid to create conditions that simulate the acidity found in a baby's stomach – which results in a cancer-killing effect.

'So far, however, it has not been proven that the Hamlet complex is spontaneously formed in the milk,' said Prof Karlsson.

'It is speculated, however, that Hamlet can form in the acidic environment of babies' stomachs.'

The researchers believe the active effect of the substance after exposure to stomach acid may contribute to the known protective effect of breastfeeding against childhood tumours.

They stressed that the development of an anti-cancer treatment based on Hamlet depends on converting it into drug form.

Read more: http://www.dailymail.co.uk/health/article-1267548/Could-acid-breast-milk-answer-beating-cancer.html#ixzz0lqfn56SQ

Findings May Alter Care for Early Breast Cancer

By **ANDREW POLLACK** Published: June 7, 2010 New York Times

CHICAGO — For many women with early-stage breast cancer, treatment may become considerably less arduous, researchers say.

new study found that certain women getting a lumpectomy may not need an operation to remove underarm lymph nodes, a procedure that can leave them with painfully swollen arms. Compared with not removing the nodes, the surgery did not prolong survival or prevent recurrence of the cancer.

And a second study found that a single dose of radiation, delivered directly to the site of the tumor right after a woman has a lumpectomy, was as effective as the six or so weeks of daily radiation treatments that most women now endure.

"We're now getting really good long-term survival for breast cancer," said Michael Baum of University College London, the lead investigator of the radiation study, which was presented here at the annual meeting of the American Society of Clinical Oncology. "The theme is now how can we improve the quality of life for women."

There is some controversy about whether women should be treated at all for certain early breast abnormalities that some experts say may never hurt them. But if a woman is to be treated, doctors would agree the treatment should be as painless and convenient as possible while retaining effectiveness.

Removal of the underarm lymph nodes next to a cancerous breast was long the standard treatment. In the 1990s doctors began to remove and examine only the sentinel node, the one to which cancer would be likely to spread first. Usually the other nodes are removed only if cancer is found in the sentinel node, which happens in about one quarter of cases.

The more extensive removal, called axillary node dissection, can cause restricted mobility of the arm and painfully swollen arms or fingers.

The study presented here involved 991 women who had had lumpectomies, radiation therapy and a positive sentinel lymph node. Half had the other lymph nodes removed and the others did not.

After five years there was no difference in survival or disease recurrence between the two groups. Some 82.2 percent of the women who had the dissection were alive and disease free compared with 83.8 percent of those who did not. Cancer recurred in the breast or nearby in 4.3 percent of those who had the operation and 3.4 percent in those who did not.

"The evidence is overwhelming that the operation might not be necessary," the lead investigator, Dr. Armando Giuliano of the John Wayne Cancer Institute in Santa Monica, Calif., said.

About a quarter of women had cancer in the nodes other than the sentinel one, based on the results from those who had the nodes removed. But somehow, this residual cancer did not hurt the patient. That is perhaps because of the radiation the women received. For that reason, Dr. Giuliano said, the results of the study apply only to women who undergo a lumpectomy followed by radiation, not women who undergo complete breast removal, who do not typically get radiotherapy.

One shortcoming was that the trial enrolled only about half the number of patients intended, limiting its ability to draw conclusions. Dr. Giuliano said doctors and patients were reluctant to participate because they feared forgoing node dissection would endanger lives.

Dr. Jennifer K. Litton, a breast cancer specialist at the M. D. Anderson Cancer Center in Houston, said the results could change practice but added, "I don't think this is going to change overnight."

She said the study involved only women with tumors that had a relatively favorable prognosis and longer follow-up was needed because cancer can recur after five years.

The radiation study tested a procedure that uses a probe to deliver a high dose of radiation directly into the breast where the tumor has been removed by lumpectomy and while the woman is still under anesthesia. Some women undergo a mastectomy instead of more limited breast-conserving surgery because they do not want the weeks of radiation therapy or live too far from a radiation center.

Dr. Dennis R. Holmes of the University of Southern California, who was one of the investigators in the trial, said one of his patients ran a marathon two weeks after getting the one-time shot of radiation. "That would have been very unlikely in someone receiving standard breast radiotherapy," he said.

The study involved 2,232 women. After about four years, there were six recurrences within the affected breast in the women who received the single-dose, or intraoperative, radiation and five cases among those who received conventional radiotherapy.

Statistically, the experimental procedure was "non-inferior" to the standard practice. The frequency of major toxicity was similar in the two groups, the authors reported in The Lancet, which published the study online on Saturday. The trial was designed by academic investigators and mainly paid for by University College London Hospitals and the British and German governments. Carl Zeiss, the company that makes the machine used, picked up some expenses. Dr. Baum, the lead investigator, is a consultant to the company.

Dr. Bruce G. Haffty, chairman of radiation oncology at the Robert Wood Johnson Medical School in New Jersey, said "the follow-up isn't as long as you'd like it to be." He said cancer can recur after four years and a large dose of radiation can cause tissue damage that might not show up for three to 10 years.

An earlier version of this article ambiguously described the nature of a lumpectomy. The wording has been clarified.

A version of this article appeared in print on June 8, 2010, on page D1 of the New York edition.

How Ethnicity and Inherited Genes Contribute to Breast Cancer Risk -- Best Approaches to Prevention and Treatment

ScienceDaily (Aug. 3, 2011) — A woman's ethnicity as well as her genetic makeup are two of the main risk factors for hereditary breast cancer. Research into understanding and treating hereditary breast cancer will be presented today at the Era of Hope conference, a scientific meeting hosted by the Department of Defense Breast Cancer Research Program (BCRP).

About 5 to 10 percent of breast cancers are thought to be hereditary, resulting from defective genes inherited from a parent. The most common cause of hereditary breast cancer is an inherited mutation in the BRCA1 or BRCA2 gene; the risk may be as high as 85 percent for members of some families with these mutations. And while White women are more likely to develop breast cancer, African American women are more likely to die from the disease, partly because African Americans have more aggressive tumors. Studies presented at Era of Hope explore the genes that contribute to breast cancer risk in African Americans, and the possibility that vitamin D intake might help mitigate it in this population. Other studies look at how daughters of women with BRCA 1 or BRCA2 mutations manage their own risk of breast cancer, and how the identification of a particular gene might lead to treatment for the very deadly triple-negative breast cancer.

"Some women are born with a greater risk of developing more aggressive forms of breast cancer," said Captain Melissa Kaime, M.D., Director of the Congressionally Directed Medical Research Programs (CDMRP), under which the BCRP is managed. "Research presented at the Era of Hope provides new insights into the specific gene mutations that lead to this risk, enabling us to develop targeted treatments and to better assist those women to manage their inherited predisposition to the disease."

Toward Understanding Genetic Susceptibility for Breast Cancer in Women of African Ancestry

Principal Investigator: Christopher Haiman, ScD, University of Southern California

Studies of genetic links to breast cancer have been conducted almost exclusively in populations of European ancestry and have firmly established a number of gene locations that are associated with breast cancer susceptibility. While these discoveries provide support for the theory that many genes can predispose someone to cancer, and provide clues to important biological pathways involved in the development of cancer, the degree to which these genetic associations can be generalized broadly to other racial/ethnic populations is unclear. A genome-wide association study among women of African ancestry was initiated to identify additional genetic risk factors for breast cancer in this population.

As a first step, this study examined genetic variation at all 18 genetic regions previously associated with breast cancer risk to both improve the current set of risk markers in African Americans and to identify new variants that may be associated with risk. Through fine-mapping, markers were identified that better define the association in African Americans in seven regions. Among them, three showed evidence of independent signals. All together, these risk markers allow for an improved ability to predict the risk of breast cancer development for African Americans over previously-reported markers.

"We are encouraged by these findings, as we continue to learn more about genetic susceptibility to breast cancer in African American women," said Dr. Christopher Haiman of the University of Southern California. "We look forward further research aimed at identifying risk variants for breast cancer in this population, in particular those for estrogen receptor negative disease which has a greater incidence among women of African ancestry. We are also working to further develop and validate this risk model to improve breast cancer risk prediction in this population using risk variants."

What Do Young Adult Daughters of BRCA Mutation Carriers Know About Hereditary Risk and How Much Do They Worry

Principal Investigator: Andrea Farkas Patenaude, PhD, Dana-Farber Cancer Institute

Women with BRCA1 or BRCA2 gene mutations have a 50 percent chance of passing the mutation and its associated high risks for breast and ovarian cancer along to their daughters. Mutations in either of these genes increase the risk of breast cancer by 85 percent (which often occurs at unusually young ages), and ovarian cancer risk by up to 60 percent. The ability of daughters of mothers who are BRCA1 or BRCA2 mutation carriers to make informed health decisions is dependent on them becoming knowledgeable about their risks, genetic testing and options for screening and risk-reducing surgery. This study uncovers the genetic knowledge, attitudes, health behaviors and life plans of daughters, ages 18-24 years, of mothers who are BRCA1 or BRCA2 mutation carriers. Data from the study will define specific health educational, psychological, insurance and medical needs of this population.

Written questionnaires and telephone interviews revealed that the young women in this study lacked knowledge about hereditary breast or ovarian cancer genetics when compared with women who had undergone genetic counseling. Further, the young women exhibited a limited understanding of screening and risk-reduction options and of the recommended age for initiating screening. Worry about hereditary breast or ovarian cancer was high among daughters, with about a third scoring above cut-offs on the Impact of Event Scale, which measured their distress related to knowledge of hereditary cancer. In addition, 40 percent of the young women reported that they worried a great deal or to an extreme about hereditary cancer.

"Young, high-risk women have little knowledge about the probabilities and options for managing the cancers for which their risks are remarkably increased. Further, many report intense anxiety related to their potential cancer development," said Dr. Andrea Farkas Patenaude of the Dana Farber Cancer Institute. "These data support the need and can provide the foundation for the development of targeted educational materials to reduce that anxiety and ultimately improve

participation in effective screening and risk-reducing interventions that can improve survival and quality of life for these young women."

Vitamin D and Breast Cancer in African American and European American Women

Principal Investigator: Song Yao, PhD, Roswell Park Cancer Institute, Buffalo

Low levels of vitamin D are thought to be linked to increased risk of breast cancer, particularly the triple-negative (TN) subtype. With TN breast cancer, cells test negative for estrogen receptors (ER-), progesterone receptors (PR-), and the HER2 (HER2-) gene, making the cancer unresponsive to the currently available hormonal or HER2 targeted treatments. African American (AA) women typically have significantly lower levels of vitamin D than their European American (EA) counterparts, potentially accounting for the strikingly high incidence of TN breast cancer among this group. This study observed the associations between the level of vitamin D and the TN status of the patients, and also examined single nucleotide polymorphisms (SNPs) in the vitamin D receptor (VDR) gene. SNPs are genetic variations in a single DNA molecule that can have a major impact on risk of diseases and response to treatments.

Women with breast cancer showed lower levels of vitamin D than women without cancer (22.8 versus 26.2 ng/mL), and those with TN breast cancer before menopause had the lowest levels (17.5 ng/mL). For each 10 ng/mL increase in vitamin D, there was a 64 percent reduction in the risk of having TN breast cancer. The prevalence of severe vitamin D deficiency (< 10 ng/mL) was almost six times higher in African American women than that in European American women (34.3 percent vs 5.9 percent). Two SNPs were found to explain, in part, the higher risk of ER-negative breast cancer in AA women.

"Our results indicate that blood levels of vitamin D are inversely linked with the risk of breast cancer, particularly TN type, which is more common in African American women and is known to have poorer prognosis." said Dr. Song Yao of Roswell Park Cancer Institute. "To our knowledge, this is the first study to indicate that vitamin D and related genetic variants may account, in part, for breast cancer racial disparities. Future work is warranted to investigate whether these disparities can be mitigated, to some extent, by maintaining sufficient levels of vitamin D."

This work was also supported by a Breast Cancer Research Foundation award to Dr. Christine Ambrosone, co-investigator on this project.

Identification of Genes Required to Suppress Tumor Transformation in Triple Negative Breast Cancer

Principal Investigator: Stephen Elledge, PhD, Brigham and Women's Hospital

Subtypes of breast cancer are generally diagnosed based on the presence or absence of three receptors that play important roles in breast cancer -- estrogen receptors, progesterone receptors, and human epidermal growth factor receptors. The triple-negative (TN) subtype is characterized by the absence of all three of these receptors and does not respond to current targeted breast

cancer therapies. African American women are at a greater risk of developing TN breast cancer than less aggressive subtypes of breast cancer. Dr. Stephen Elledge and colleagues recently identified a gene, PTPN12 tyrosine phosphatase, as a tumor suppressor in women with TN breast cancer. PTPN12 suppresses the growth and transformation of mammary epithelial cells in breast tissue, and is frequently compromised in TN breast cancer. Restoring PTPN12 function in deficient TN breast cancer cells can block their ability to form tumors and become metastatic. This effect is also seen in cells with inhibition of PTPN12-regulated tyrosine kinases thus suggesting that TN breast cancer cells are dependent on proto-oncogenic tyrosine kinases constrained by PTPN12.

"Our data suggests that PTPN12 is commonly inactivated in triple-negative breast cancer and results in activation of cellular tyrosine kinases which could be targets for this intractable cancer," said Dr. Elledge. "While we are still understanding the triple-negative subtype, our research findings could play a key role in improving the treatment of this disease."

Story Source:

Breast Cancer

Updated: 06/15/2004

Most women share a common fear: developing breast cancer. This is not an unfounded fear when considering that, except for lung cancer, breast cancer is the most common cancer found in women, accounting for one of every three diagnoses. However, men are also affected by breast cancer. In 2002 the American Cancer Association estimate that 1500 men will be diagnosed with breast cancer, and 400 will die as a result. In 2001 an estimated 192,200 American women were diagnosed with breast cancer and 39,600 women died of the disease (The American Cancer Association). In 2004 an estimated 203,500 new cases of breast cancer will be diagnosed in America.

WHAT IS BREAST CANCER?

Breast cancer occurs when cells in the breast tissue divide and grow without control. The cell cycle is the natural mechanism that regulates the growth and death of cells. When the normal cell regulators malfunction and cells do not die at the proper rate, there is a failure of cell death (apoptosis) therefore cell growth goes unchecked. As a result, cancer begins to develop as cells divide without control, accumulating into a mass of extra tissue called a tumor. A tumor can be either non-cancerous (benign) or cancerous (malignant). As a tumor grows, it elicits new blood vessel growth from the surrounding normal healthy tissues and diverts blood supply and nutrients away from this tissue to feed itself. This process is termed "angiogenesis"- the development (genesis) of new blood vessels (angio). Unregulated tumor angiogenesis facilitates the growth of cancer throughout the body.

Cancer cells have the ability to leave the original tumor site, travel to distant locations, and recolonize. This process is called metastasis and it occurs in organs such as the liver, lungs, and bones. Both the bloodstream and lymphatic system (the network connecting lymph nodes throughout the body) serve as ideal vehicles for the traveling cancer. Although, these traveling cancer cells do not always survive beyond the tumor, if they do survive, the cancer cells will again begin to divide abnormally and will create tumors in each new location. A person with untreated or treatment-resistant cancer may eventually die of the disease if vital organs such as the liver or lungs are invaded, overtaken, and destroyed.

Cancerous tumors in the breast usually grow slowly. It is thought that by the time a tumor is large enough to be felt as a lump, it may have been growing for as long as 10 years. This has lead to the belief that undetectable spread of tumor cells (micrometastasis) may have already occurred by the time of the diagnosis. Therefore, preventive measures such as a healthy balanced diet and lifestyle, nutritional supplementation, and exercise are of primary importance against the development of cancer. Early diagnosis is the best way to reduce the risk of dying from breast cancer. This can be accomplished by monthly self-breast exams, annual clinical breast exams and screening mammography. If breast cancer is detected, a multimodality approach incorporating nutritional supplementation, dietary modification, detoxification, and one or more of the following may be considered: surgery, chemotherapy, radiation, hormone therapy, or vaccine therapy.

RISK FACTORS

A wide variety of factors may influence an individual's likelihood of developing breast cancer; these factors are referred to as risk factors. The established risk factors for breast cancer include: female gender, age, previous breast cancer, benign breast disease, hereditary factors (family history of breast cancer), early age at menarche (first menstrual period), late age at menopause, late age at first full-term pregnancy, obesity, low physical activity, use of postmenopausal hormone replacement therapy, use of oral contraceptives, exposure to low-dose ionizing radiation in midlife and exposure to high-dose ionizing radiation early in life.

Correlated risk factors for breast cancer include never having been pregnant, having only one pregnancy rather than many, not breast feeding after pregnancy, diethylstilbestrol (DES), certain dietary practices (high intake of fat and low intakes of fiber, fruits, and vegetables), tobacco, smoking, abortion, breast trauma, breast augmentation, large breast size, synthetic estrogens, electromagnetic fields, use of nonsteroidal anti-inflammatory drugs (NSAIDs), and alcohol consumption. Alcohol is known to increase estrogen levels. Alcohol use appears to be more strongly associated with risk of lobular carcinomas and hormone receptor-positive tumors than it is with other types of breast cancer (Li et al. 2003).

A novel growth inhibitor recently identified as estrogen down-regulated gene 1 (EDG1) was found to be switched off (down-regulated) by estrogens. Inhibiting EDG1 expression in breast cells resulted in increased breast cell growth, whereas over-expression of EDG1 protein in breast cells resulted in decreased cell growth and decreased anchorage-independent growth, supporting the role of EDG1 in breast cancer (Wittmann et al. 2003).

ANATOMY OF THE BREAST

The breast is composed mainly of fat (adipose tissue) and breast tissue, along with connective tissue, nerves, veins, and arteries. Breast tissue is a complex network known as the mammary gland. Within the mammary gland, there are 15-20 lobes or compartments separated by adipose tissue. Within each lobe are several smaller compartments called lobules.

Lobules are composed of grapelike clusters of milk-secreting glands termed alveoli, which are found embedded in connective tissue. Spindle-shaped cells called myoepithelial cells, whose contractions help propel milk toward the nipple, surround the alveoli. There are about one million lobules contained within each breast (Spratt et al. 1995). The lobules are connected by tiny ducts that are joined together (much like a grape stem) into increasingly larger ducts. Within each breast there are between five and ten ductal systems, each with its own opening at the nipple.

Surrounding the nipple is a darkly shaded circle of skin called the areola. The areola appears rough because it contains modified sebaceous (oil) glands. These glands secrete small amounts of fluid to lubricate the nipple during breast-feeding.

Of all breast cancers, about 80% originate in the mammary (lactiferous) ducts, while about 20% arise in the lobules (IOM 1997). One of the most important distinctions to understand is the difference between invasive breast cancer and carcinoma in situ.

TYPES OF BREAST CANCER

- Invasive Cancer
- Carcinoma In Situ
- Ductal Carcinoma In Situ
- Lobular Carcinoma In Situ

Invasive Cancer
When abnormal cells from within the lobules or mammary ducts break out into the surrounding tissue the condition is referred to as invasive breast cancer. However, this term does not necessarily mean that metastases have been found anywhere beyond the breast.

Carcinoma In Situ
Carcinoma in situ is referred to as precancerous condition because it can increase the risk of developing cancer. When abnormal cells grow within the lobules or mammary ducts and there is no sign that the cells have spread into the surrounding tissue or beyond, the condition is called carcinoma in situ. The term in situ means "in place". There are two main categories of carcinoma in situ: ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS).

Non-invasive cancer is grouped into four subcategories, based on how the cancer cells grow relative to each other within the center

of the milk duct:

Solid: There is wall-to-wall cell growth

Cribiform: There are holes between groups of cancer cells, making it look like Swiss cheese.

Papillary: The cells grow in fingerlike projections, toward the inside of the duct.

Comedo: There are areas of "necrosis," which is debris from dead cancer cells; this indicates that a tumor is growing so fast that some tumor cells die because there is insufficient blood supply.

Carcinoma in situ is generally considered a slow-growing cancer. The solid, cribiform, and papillary growth patterns are also referred to as "low-grade" cancers. However, Comedo is considered a faster growing cancer and is referred to as a "high-grade" non-invasive cancer, but is more likely than other categories to become invasive.

Ductal Carcinoma In Situ
Mammary ducts are hollow to allow fluid to pass through. However, with ductal carcinoma in situ (DCIS) excess cells grow inside the mammary ducts. DCIS is not invasive cancer. It is a precancerous condition that has the potential to develop into breast cancer. DCIS is, however, a risk factor for breast cancer.

Lobular Carcinoma In Situ
The lobules of the breast tissue have open space inside them much like the mammary ducts. Lobular carcinoma in situ (LCIS) is the growth and accumulation of large numbers of abnormal cells within the lobules. LCIS is often referred to as lobular neoplasia in situ. LCIS is not a direct cancer precursor. The abnormal cells found inside the lobules are not likely to mutate into cancer. LCIS is, however, a risk factor for breast cancer.

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SPECIAL MANIFESTATIONS OF CANCER

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- Paget's Disease of the Nipple
- Inflammatory Breast Cancer

Paget's Disease of the Nipple
Paget's disease is a rare, slowly growing cancer of the nipple. Paget's disease is usually associated with in situ or invasive cancer. One of the biggest problems with Paget's disease of the nipple is that its symptoms appear to be harmless. It is frequently thought to be a skin inflammation or infection, leading to unfortunate delays in disease detection, diagnosis and treatment. Symptoms of Paget's disease include persistent redness, itching, oozing, crusting, and fluid discharge from the nipple or a sore on the nipple that does not heal. Typically, only one nipple is affected. Treatment and prognosis for the disease are directly related to the type and extent of the underlying cancer.

Inflammatory Breast Cancer (IBC)
Inflammatory breast cancer (IBC) is a rare and aggressive form of invasive breast cancer that is usually not detected by mammograms or ultrasounds. IBC usually grows in nests or sheets rather than as a confined solid tumor and can be diffuse throughout the breast with no palpable mass. The cancer cells clog the lymphatic system just below the skin, resulting in lymph node involvement. Increased breast density compared to prior mammograms should be considered suspicious.

However, the main symptoms of IBC are breast swelling, inflammation, pink, red, or a dark colored area (erythema), sometimes with texture similar to the skin of an orange (peau d'orange), ridges and thickened areas of the breast skin, an area of the breast that is warm to the touch, what appears to be a persistent bruise, itching (pruritus) that is unrelenting and unaffected by medicated creams and ointments, increase in breast size over a short period of time, nipple flattening, retraction, or discharge, breast pain that is not cyclic in nature and may be constant or stabbing, or swollen lymph nodes in the armpit or above the collar bone. Since many of these symptoms mimic a breast infection, doctors frequently treat inflammatory breast cancer merely as an infection. When symptoms do not improve after antibiotic treatment for the suspected "infection" only then is the inflammatory breast cancer diagnosed.

IBC has an extremely high risk of recurrence and a very poor prognosis. It is the most lethal form of breast cancer. To improve the chances of survival it is important that symptoms are recognized early, resulting in an immediate diagnosis and treatment.

Chemotherapy is usually begun within days of diagnosis. Without treatment, chances of 5-year survival for individuals with inflammatory breast cancer are very poor. With treatment, about 50% of patients will be living 5 years after diagnosis.

BREAST DISEASES

- Calcifications
- Cysts
- Fibroadenomas
- Hyperplasia
- Atypical Hyperplasia

There are a variety of breast diseases, ranging from infections to excessive cell growth (neoplasms). Unfortunately, many breast diseases mimic the symptoms of cancer and therefore require tests and possibly surgical biopsy to obtain an accurate diagnosis. The majority of biopsies are found to be benign (non-cancerous) forms of breast disease. While most breast diseases are not dangerous in themselves, they may increase the risk of developing breast cancer. Hyperplasia, cysts, fibroadenomas, and calcifications are the common benign breast diseases.

Calcifications
Calcifications are randomly scattered residues of calcium that in older women may have left the bones to appear in other parts of the body, such as the joints or breasts. Microcalcifications are small, tight clusters of tiny calcifications in the ducts that can be seen on a mammogram and may indicate a precancerous or cancerous condition.

Cysts
Cysts are sacs filled with fluid; they are almost always benign. Although most are too small to feel, approximately a third of women between the ages of 35-50 have cysts in their breasts. If large enough, cysts may feel like lumps in the breast. Normally, cysts are left untreated. However, if a cyst becomes painful, it can be aspirated or drained of its fluid. Some women may prefer to have a cyst removed if, after being aspirated repeatedly, it continues to recur.

Cysts are not associated with an increased risk of cancer; yet, they are more common in women as they approach menopause and occur much less frequently after menopause (Donegan 1995). What causes cysts to develop is unknown; however, certain dietary factors, such as the intake of caffeine have been proposed as possible risk factors for the development of breast cysts.

Fibroadenomas
Fibroadenomas are a type of benign lump most commonly found in younger women. They are usually not removed since they pose no risk. If a fibroadenoma is large, uncomfortable, and produces a lump, it may be removed. In older women, fibroadenomas are generally removed to ensure that they are not malignant tumors. Fibroadenomas do not pose an increased risk of cancer.

Hyperplasia
Hyperplasia is not a precancerous condition. It is the excessive accumulation or proliferation of normal cells typically found on the inside of the lobules or the ducts in the breast tissue. Hyperplasia is associated with approximately a two-fold risk of breast cancer.

Atypical Hyperplasia
Atypical hyperplasia occurs when excess cells in the lobules or ducts are abnormal. This condition falls between hyperplasia (too many normal cells) and carcinoma in situ (too many abnormal cells). However, atypical hyperplasia is associated with an approximately 3.5-5 times increased risk of developing breast cancer (Page et al. 1985; Colditz 1993; Marshall et al. 1997).

Breast Cancer

TYPES OF STANDARD SCREENING TECHNIQUES

- Breast Self-Exam
- Clinical Breast Exam
- Mammography
- Ultrasound
- MRI
- Thermography
- High-Risk Screening

In order to detect breast cancer at its earliest, most treatable stage, the importance of regular monthly breast self-exams, and yearly clinical breast exams, cannot be overemphasized. Mammography, sonography, contrasting magnetic resonance imaging (MRI) and digital infrared thermal imaging are all viable diagnostic tools, which will be discussed later in this article. Having regular breast-cancer screening exams is considered the single most effective way to lower the risk of dying from breast cancer.

"Early-stage" invasive cancer is considered very treatable because the tumor is relatively small and the cancer cells have not spread to the lymph nodes. However, when a tumor has become very large or has spread to other organs (such as the liver, lungs, or bones), it is considered "advanced-stage" invasive cancer and is far less treatable.

Breast cancer was thought to grow in an orderly progression from a small tumor in the breast tissue to a larger tumor. The cancer was believed to then travel from the breast into the adjacent lymph nodes, spreading throughout the distant nodes and finally metastasizing in other areas of the body. However, a growing body of research now contends that cancer cells are capable of traveling from the breast throughout the blood and lymphatic systems very early in the course of the disease. This strengthens the rationale for early detection and treatment.

Breast Self-Exam

- How to Do Breast Self-Exam **(7A1)**

A breast self-exam provides an opportunity to detect tumors that may develop in the time between yearly clinical breast exams. To increase a woman's chances of detecting a small tumor at a time when it may be more responsive to treatment, a breast self-exam should be performed monthly, usually 2-3 days after menstruation. For women with irregular periods, it is important to remember to perform a monthly exam on the same day each month. Keep in mind that prior to menstruation or during pregnancy, breasts may be somewhat lumpy or more tender than usual.

By performing self-exams once a month, women can become familiar with the normal appearance and "feel" of their breasts, increasing the likelihood of recognizing changes such as thickening, lumps, or spontaneous nipple discharge. Because breast tissue normally has a bumpy texture, it may feel lumpy. However, there can be a great deal of individual variation. If a breast has lumpiness throughout, then it is probably just the normal contours of the breast tissue and in most cases is no cause to worry. Dominant lumps are firmer than the rest of the breast and are of more concern. When a dominant lump is found, there is an increased risk that it may be cancer, even though cysts and fibroadenomas can cause similar lumps. Any time a woman discovers a lump that feels dominant, it should be checked by a medical professional.

How to Do Breast Self-Exam

1. Lie down. Flatten your right breast by placing a pillow or towel under your right shoulder. Place your right arm behind your head. Examine your right breast with your left hand.
2. Use the pads, not the tips, of the middle three fingers on your left hand. With fingers flat, press gently using a circular, rubbing motion and feel for lumps. In small, dime-sized circles without lifting the fingers, start at the outermost top edge of your breast and spiral in toward the nipple.
3. Press firmly enough to feel the different breast tissues, using three different pressures. First, light pressure to just move the skin without jostling the tissue beneath, then medium pressure pressing midway into the tissue, and finally deep pressure to probe more deeply down to the ribs or to the point just short of discomfort.
4. Completely feel all of the breast and chest area up under your armpit, up to the collarbone, and all the way over to your shoulder to cover breast tissue that extends toward the shoulder.

5. Gently squeeze both nipples and look for discharge.

After you have completely examined your right breast, examine your left breast using the same method with your right hand. You may want to examine your breasts or do an extra exam while showering. It's easy to slide soapy hands over your skin and to feel anything unusual. You should also check your breasts in a mirror, looking for any change in size or contour, dimpling of the skin, or spontaneous nipple discharge.

Clinical Breast Exam

Clinical breast exams are physical examinations to check the appearance and "feel" of the breasts for signs of lumps. A physician, nurse practitioner, or other trained medical staff person will examine the breasts, both when the woman is sitting upright and when she is lying down.

Clinical breast exams are an important part of breast cancer screening. For younger women, clinical breast exam may have an advantage over mammography; mammography images can be more difficult to read in some younger women because of their dense breast tissue. For this reason, clinical breast exams are generally started much earlier than mammograms.

Mammography

Mammography is an x-ray technique used to locate small or indistinctly shaped breast lumps that may not be felt during an exam. A mammogram takes about 15 minutes and consists of compressing each breast individually between two plates to makean x-ray image. Afterwards, a radiologist will read the film and look for any signs of abnormal tissue.

X-ray images appear in gradations of black, gray, and white depending on the density or hardness of the tissue. For example, since bone is especially dense, it appears white on an x-ray, while fat appears dark gray. Cancerous tumors and some other noncancerous abnormalities appear as a lighter shade of gray. Unfortunately, this may pose a problem because normal, dense breast tissue may appear light gray on a mammogram. Breast density changes with age. Younger women have proportionately more breast tissue than fat and therefore denser breasts, making mammograms difficult to interpret. In older women's breasts, density dissipates with age, leaving breasts that are composed mostly of fat. A mammogram that shows the light gray patch of a tumor or lesion surrounded by the dark gray image of fat tissue is most easily recognized.

Cysts and fibroadenomas appear as circular or oval patches with stark outer edges on x-rays, allowing a radiologist to identify where the border of the benign abnormal tissue ends and the surrounding normal tissue begins. On an x-ray, the core cancerous cells appear as a light patch, while the cancer cells that invade the surrounding tissue create a fuzzy or spiky appearance along the outer edge (called "spiculated"), producing an image with no clear borders.

There is growing controversy regarding the safety and efficacy of mammography. The National Cancer Institute clearly states on their website "Being exposed to radiation is a risk factor for breast cancer" (National Cancer Institute 2003). Further, both low-filtered (30 kVp) x-rays and mammography x-rays have mutagenic effect on mammalian cells. A re-evaluation of the risk assessment of mammography, especially for familial predisposed women is recommended. People with known increased risk of breast cancer, particularly those with a familial predisposition, are advised to be cautious and avoid early and frequent mammography exposure. Alternative examination methods should be considered for women with an inherited increased risk of breast cancer (Frankenberg-Schwager et al. 2002).

There is evidence that high-quality mammography may reduce breast cancer mortality in women aged 50 to 69. In fact, the risk of radiation-induced breast cancer decreases with increasing age at radiation exposure (Jung 2001). There has been difficulty in establishing the benefit of screening mammography in younger women. This difficulty has been attributed to both the technical limitations introduced by younger women's dense breast tissue and to differences in breast cancer biology in younger women. Equally, women with inherited increased risk for breast cancer may gain no benefits from early screening.

The false positive rate ranges from 2.6% to 15.9% (Elmore et al. 2002). False positives usually result in additional diagnostic tests, which can include an additional x-ray examination, or a biopsy, which is the removal of a small portion of breast tissue for microscopic examination. A portion of the population's mammograms are misread as false negatives. A false negative mammogram occurs when the mammogram is read as "normal" or "negative" although a malignancy is present. Screening mammograms from a population-based screening registry estimated a missed detectable cancer rate of 29% (Yankaskas et al. 2001). Other studies report a missed detectable cancer rate by mammograms of approximately 12% to 37% (Woolf 2001).

Regardless of the high rates of false-positives and false-negatives, x-ray mammography is still considered the gold standard of breast cancer screening since it can detect tumors at an early stage when they are small and responsive to treatment. Most physicians recommend annual mammograms for women over 40, and for those at high risk with a family history of breast cancer.

Ultrasound

Ultrasound, also known as sonography, is an imaging method that utilizes very-high frequency sound waves to produce a picture that outlines the breast without exposure to ionizing radiation. During a sonogram, (also known as echogram) sound waves are transmitted through the breast. Depending on the nature of the breast tissue, the sound waves are reflected back or are transmitted through the tissue being examined. The pictures generated are the results of such echoes; they are picked up and translated by a computer resulting in the ultrasound image. Breast ultrasonography can be used to evaluate breast problems found during a mammogram or a physical exam.

Ultrasound is useful for some breast masses. It can be used to determine if a breast mass is solid (and more likely to be malignant) or if it is cystic and filled with fluid (and more likely to be benign). The ultrasound facilitates analysis by enabling the radiologist to guide a needle to biopsy a solid mass or to remove fluid if it is a cystic fluid-filled mass. The limitation of both mammography and ultrasound is that both have diagnostic features, which depend primarily on structural distinction and anatomical variation of a tumor from the surrounding breast tissue. These limitations make distinguishing benign microcalcifications from malignancies nearly impossible.

MRI

Magnetic Resonance Imaging (MRI) of the breast, also known as a breast MRI, is an imaging method consisting of a high field (1.5 Tesla) magnet with dedicated breast coils linked to a computer. The most useful MRI breast examination combines a contrast material, known as Gadolinium DTPA, magnetization, and radio waves to provide detailed pictures of an area inside the breast by a computer without the use of radiation. Every MRI produces hundreds of images of the breast from side-to-side, top-to-bottom, and front-to-back.

MRI is the most sensitive imaging modality for detection of breast cancer (Kuhl et al. 2000; Warner et al. 2001). Unfortunately, an MRI cannot always accurately distinguish between cancer and benign (noncancerous) breast conditions. Like ultrasound, MRI cannot detect microcalcifications. MRI is, however, effective in evaluating dense breast tissue and may be useful in screening younger women at high risk for breast cancer due to a predisposing family history of breast cancer.

MRI can be used to evaluate women who have had augmentation or breast enlargement surgery using implants. In such context, MRI is an excellent tool for imaging the augmented breast, including the breast implants itself, and the surrounding tissue, since abnormalities or signs of breast cancer are sometimes obscured by the implant. In contrast, the x-rays used in mammography are not able to penetrate silicone or saline implants sufficiently to image the overlying or underlying breast tissue. Compared to mammography or ultrasound, MRI is more accurate in women with augmented breasts.

Thermography

Digital Infrared Thermal Imaging, also known as thermography, is a painless, non-invasive diagnostic technique, which does not involve any radiation exposure. This technology at one time appeared promising but lost favor about 20 years ago. However, with new ultra-sensitive high-resolution digital infrared devices, its efficacy has been improved. Infrared imaging software utilizes high precision pixel temperature measurements which can detect minute temperature variations related to blood flow and can demonstrate abnormal blood flow patterns associated with the initiation and progression of a chaotic tumor vasculature (blood flow system). Angiogenesis is a key factor that facilitates the growth of cancer and it is this biological feature of cancer on which thermography is based. Due to thermography's sensitivity to blood flow and metabolic changes, it can detect tumors at a smaller size than mammography.

Unfortunately, there are no studies involving the detection of breast cancer that compare the accuracy of Digital Infrared Thermal Imaging to that of mammography, ultrasound, and MRI. However, studies have been conducted to evaluate the accuracy of mammography versus ultrasound versus MRI. In a study that screened 192 women at high risk for breast cancer, cancer was detected in nine patients. Mammography and ultrasound detected 6 of the nine cases of cancer whereas MRI detected all nine cases of breast cancer (Kuhl et al. 2000).

Another study comparing the accuracy of these three modalities screened 196 women at high risk for hereditary breast cancer and detected a total of six cases of invasive breast cancer. Mammography detected 2 of the 6 cases, ultrasound detected 3 of the 6, and MRI detected all 6 cases(Warner et al. 2001).

High-Risk Screening

Regular screening is especially important for women who are at high risk of breast cancer. A woman can be placed in a high-risk category if she possesses either a single factor that greatly increases her risk or a combination of lesser factors that together increase her risk.

Single factors that can place a woman in a high-risk category include a personal history of breast cancer, carcinoma in situ,

atypical hyperplasia, and exposure to high doses of ionizing radiation in childhood or young adulthood (for instance, for treatment of Hodgkin's disease) (Hancock et al. 1993; USPSTF 1996; Harris et al. 1997). A family history of breast cancer, especially in a mother, sister, or daughter, or a particular genetic mutation can also place a woman at high risk of breast cancer. In addition, research on genetic markers for breast-cancer risk has pinpointed a number of genes, two of which, BRCA1 and BRCA2, are associated with a markedly elevated risk of breast and ovarian cancer. As many as 60-80% of women with mutations in either of these two genes may develop breast cancer in their lifetimes (Alberg et al. 1997; Struewing et al. 1997; Whittemore 1997).

There are also several moderate risk factors for breast cancer, which occurring together can place a woman at high risk. They include having a first period (menarche) before age 12, not bearing a child, and having a first child after age 30. It is recommended that women at high risk for breast cancer have annual clinical breast examinations more frequently than women at average risk.

Breast Cancer

TYPES OF ABNORMAL SCREENING FINDINGS

- From a Clinical Breast Exam
- Needle Biopsy
- Other Abnormal Findings from a Clinical Breast Exam
- Abnormal Findings from a Mammogram

Typically, a clinical breast exam or mammogram will show no sign of disease. However, for some women, the test results will prove to be abnormal, and they will need to have additional tests to determine whether they have cancer. Which tests are performed depends on a number of factors, such as the type of abnormality found and the age of the woman. Usually the follow-up tests begin with the least invasive methods, such as an ultrasound or second mammogram, and progress, if necessary, to the more invasive methods, such as a needle or surgical biopsy. A biopsy should spare the tissue, removing just enough tissue to make a diagnosis without being unnecessarily invasive. A woman should not rush from one abnormal screening mammogram or clinical breast exam to a major invasive surgical procedure or to treatment for breast cancer. Following the series of tests outlined below may help avoid unnecessary procedures.

From a Clinical Breast Exam

- For Individuals Age 30 and Older

A lump called a palpable mass is the most common abnormal finding from a clinical breast exam. The first determination that must be made is whether the mass is solid or fluid-filled. Most likely, if it is fluid-filled, the mass is a cyst. Simple fluid-filled cysts are not cancerous and can be left untreated in many cases. However, complex cysts contain both solid tissue and fluid and may need additional examination to assure they are not cancerous. Solid masses, on the other hand, are potentially cancerous.

For Individuals Age 30 and Older
The general approach to follow up a palpable mass involves further examination of the mass with a diagnostic mammogram, ultrasound, or needle biopsy. Mammography with or without an ultrasound is often the first choice. However, a person with a mass that is likely not cancerous may choose to begin follow-up with a needle biopsy. Instead of an initial needle biopsy, most individuals with a palpable mass begin follow-up tests with a mammogram and/or ultrasound of the mass. This imaging may help avoid a needle biopsy by identifying a mass as a simple cyst, complex cyst, or a suspicious mass that could be cancerous.

Needle Biopsy

- For Individuals Under Age 30

A needle biopsy is the insertion of a thin, hollow needle into a breast mass to ascertain if fluid can be drawn out (aspirated). If fluid can be aspirated, this indicates that the mass is a cyst. If the cyst is completely reduced after being aspirated and does not return after 2-3 months, then no further treatment is required. If the mass is not completely reduced after being aspirated or if it later returns, then additional steps are necessary to rule out cancer, including another needle biopsy, an ultrasound examination, or surgical removal of the mass.

If fluid is not aspirated during the initial needle biopsy, this is an indication that the mass is solid, and an examination of the tissue removed during the needle biopsy will determine the next step. If the mass is found to be a fibroadenoma, then the woman has a choice to make: Have it removed or have it closely monitored. Removal involves surgery, but can determine definitively whether or not there is any cancer present.

If the initial needle biopsy results are unclear, then the mass will be examined with mammography and/or ultrasound, followed by either another needle biopsy or a surgical biopsy. However, if the initial needle biopsy reveals cancer, then treatment should begin at once.

For Individuals Under Age 30
In this age group, the follow-up is slightly different because most individuals with a palpable mass have a very low rate of breast

cancer. Follow-up of a palpable mass usually begins with observing the mass for a duration of 1-2 menstrual cycles (in women) to see if it persists or disappears. During this follow-up period, clinical breast exams should not be performed in the week before or during a woman's menstrual period because cysts can become enlarged during menstruation. If the mass remains after the observation period, then an ultrasound or needle biopsy will be performed. If a woman has a strong family history of cancer (e.g., two or more immediate family members with cancer), there is increased risk of breast cancer, and an ultrasound or needle biopsy may be performed without waiting.

Other Abnormal Findings from a Clinical Breast Exam
In addition to a palpable mass, other potentially abnormal findings during a clinical breast exam include thickening within the breast, changes to the skin, and nipple discharge. Any of these abnormal findings require a follow-up to assure that they are not signs of cancer.

Abnormal Findings from a Mammogram
Nonpalpable lesions are tissue abnormalities that generally are either too small to be detected during a clinical breast exam or are spread out in such a way that there is no lump even if the mass is large. Nonpalpable lesions are typically found by mammogram.

First, the radiologist compares the mammogram with previous (or baseline) abnormal mammograms. Next, the radiologist will perform a diagnostic mammogram, focusing on the area where there appears to be abnormal tissue. An ultrasound of the area may also be performed.

The next step will be determined based upon the findings from the diagnostic mammogram and ultrasound. If the lesion is clearly not cancer (e.g., a simple cyst), there is no further follow-up necessary. If the lesion appears likely to be benign (e.g., a fibroadenoma), a repeat mammogram at 6 months and follow up at the physician's discretion is required.

A suspicious lesion can be cancerous; therefore, the next step is to perform a biopsy of the lesion, using stereotactic fine needle aspiration or core needle biopsy (both will be discussed later in this protocol). If the biopsy findings do not agree with the mammogram findings, both procedures must be repeated. If the findings are in agreement, a diagnosis can be made. If the lesion is found to be cancerous, treatment should commence immediately. If the lesion is benign, a follow-up mammogram should be performed within a year. If the follow-up mammogram reveals nothing abnormal, then a woman can return to her normal schedule of mammograms and clinical breast exams. If a lesion is a particular type of benign breast disease (e.g., atypical hyperplasia), the lesion should be excised and examined for the presence of cancer. If cancer is found, treatment should commence immediately. If no cancer is found, then a woman can return to her normal screening schedule.

TYPES OF BIOPSIES

- Core Needle Biopsy
- Fine Needle Aspiration
- Excisional Biopsy
- Wire Localization for Nonpalpable Lesions
- Frozen Sections
- Excisional Biopsy as a Surgical Treatment
- Incisional Biopsy

Two general categories of biopsies are used to diagnose breast cancer. These are:

1. Needle biopsies, which include core needle biopsy and fine needle aspiration.
2. Open biopsies, which include excisional biopsy (including wire localization) and incisional biopsy.

Core Needle Biopsy
Core needle biopsy, or cutting needle biopsy, is a method of procuring tissue samples from the breast using a thin, hollow needle. Palpable lumps can be biopsied in a doctor's office using local anesthetic. Using the fingertips to isolate the lump, the doctor makes a small nick in the skin, inserts a needle, and removes a sample of the tissue from the suspicious area. A pathologist, who microscopically evaluates the breast tissue and/or lymph nodes removed during biopsy or surgery for cancer, then examines the tissue sample.

For nonpalpable areas that cannot be felt to be sampled, the procedure is more involved and will likely be performed in a hospital or outpatient clinic because of the need for special equipment to locate and accurately sample the correct area. An ultrasound or

special three-dimensional mammography, called stereotactic mammography is used.

A core needle biopsy using stereotactic mammography entails first placing a woman on her stomach on a mammography table with the affected breast fitted through a hole in the table. The breast is compressed so that it will remain in place to record an accurate image. Calculations are made based on this image, and a biopsy device containing a needle automatically takes a number of tissue samples from the affected area in the breast. Multiple samples increase the chances of an accurate diagnosis. This procedure involves little pain because the device inserts and removes the needle very quickly.

A core needle biopsy using ultrasound entails a women lying on her back and the doctor holding an ultrasound transducer against the breast. The transducer makes an image of the area to be sampled, allowing the doctor to follow the needle as it enters the breast and reaches the abnormal area. The needle is then inserted by hand and a sample of tissue is removed.

The core needle biopsy provides several advantages. It supplies specific information about a tumor, such as whether it is in situ or invasive. It is accurate, quick, relatively inexpensive, only mildly uncomfortable, and does not involve surgery.

There are disadvantages to the core needle biopsy. The most important is that the core needle biopsy can produce false negative results. False negatives may occur if the needle misses the tumor and instead takes a sample of normal tissue. This can impact a woman's chances for long-term survival because the undiagnosed cancer may go untreated. Furthermore, the samples taken may not provide complete information about a tumor; a tumor may be diagnosed as being in situ instead of invasive. Taking multiple tissue samples can help limit this potential problem.

Fine Needle Aspiration (FNA)
Fine needle aspiration (FNA), also known as fine needle biopsy, is a method of procuring cell samples using a very thin needle. Although FNA can be performed on both palpable lumps as well as nonpalpable areas found by mammogram, FNA is recommended only for use on palpable lumps. The key to an accurate diagnosis is the removal of an adequate number of cells from the suspicious area. With nonpalpable lesions, however, FNA can frequently remove insufficient samples of cells, especially compared to core needle biopsy.

For palpable lumps, FNA can be done in a doctor's office. During the procedure, the doctor will locate and isolate the lump with the fingertips, insert a very thin needle attached to a syringe, and draw out (or aspirate) a sample of cells. The needle is so thin that there is little pain, and no anesthetic is needed. The whole procedure takes only a few minutes. Then the sample cells will be sent to a doctor or a cytopathologist who specializes in examining individual cells for a diagnosis.

The advantages of FNA are that it is quick, relatively inexpensive, only mildly uncomfortable, and does not involve surgery. FNA is an excellent method of diagnosing cancer when it is performed on a palpable lump by an experienced doctor and is analyzed by an experienced cytopathologist.

There are several disadvantages to using the FNA procedure. FNA is not recommended for nonpalpable lesions. Even for palpable masses, FNA may not remove enough cells for the cytopathologist to be able to make an accurate diagnosis. In addition, false negatives occur in about 0-4% of FNA procedures performed on palpable lesions (Harris et al. 1997). As a result, a woman having an FNA may need to have a more definitive biopsy, such as a core needle or excisional biopsy, to ensure that the palpable lesion is not cancerous.

Another drawback of FNA is that while it can be used to determine if cells are cancerous, it cannot distinguish in situ cancers from invasive cancers. However, these two types of cancers are generally treated differently via surgery. Finally, FNA requires an experienced breast cytopathologist to accurately analyze the sample of cells, a type of physician that not all hospitals or medical centers will have on staff.

Excisional Biopsy
An excisional biopsy is the most accurate method for diagnosing breast cancer. It is also referred to as "lumpectomy" or "partial mastectomy." An excisional biopsy is performed by a surgeon and is generally done under a local anesthetic, meaning that the area to be operated on is desensitized, but the patient remains awake. During the procedure, the surgeon makes an incision in the breast and removes the entire suspicious area and a small amount of surrounding normal tissue. Most women are able to have a biopsy and return home the same day.

Wire Localization for Nonpalpable Lesions
A nonpalpable lesion is difficult to locate during an excisional biopsy. Therefore, a radiologist uses a mammography or ultrasound image for direction and a surgeon inserts a very thin wire into the breast as a guide to identify the breast tissue that requires removal. The surgeon then removes the abnormal tissue. This procedure is called wire localization or needle localization.

Once the nonpalpable mass is removed, the tissue is x-rayed immediately. This allows the surgeon and radiologist to match the suspicious areas on a woman's mammogram with those in the biopsy tissue. If the areas do not match, the surgeon has two options. One option is for the surgeon to make an additional attempt to remove the correct tissue. The other option is to wait and rebiopsy at another time when the area has been targeted a second time using the wire localization technique.

Frozen Sections

Immediately after the tumor is removed from the breast, a frozen section is usually performed. This process entails freezing a portion of the biopsied tissue and then quickly cutting a thin slice for the pathologist to analyze under the microscope. In the past, if a biopsy came back as positive for cancer, surgical treatment was performed immediately. Currently, biopsies are prior to and separate from the definitive surgery. However, immediate results using frozen sections can help alleviate a woman's anxiety.

A high percentage of false negatives may be produced with frozen sections. Therefore, frozen section results are only preliminary and need to be confirmed by a routine fixed sample, which takes about 2 working days to analyze (Harris et al. 1997).

Excisional Biopsy as a Surgical Treatment

The primary function of an excisional biopsy is to diagnose cancer. However, it can also serve as definitive surgery by removing the cancerous tumor from the breast. Definitive surgery consists of the removal of the entire tumor plus a surrounding amount of normal tissue (a margin) and possibly the axillary lymph nodes.

The pathologist will then inspect the tumor margins. If normal tissue surrounds the entire tumor (which is termed clean or uninvolved or negative margins), the surgery is considered definitive and no additional surgery is needed. If there is insufficient normal tissue surrounding the tumor ("dirty" or involved or positive margins), additional surgery is required to remove the remaining tumor.

The excisional biopsy has many advantages over a needle biopsy. It provides a larger sample size, ensuring far fewer false negative results, and provides accurate information on factors such as tumor size, tumor grade, and the presence of estrogen receptors, all of which are key factors in deciding on a treatment plan.

The excisional biopsy has some disadvantages. It is a far more extensive procedure than a needle biopsy. If a large amount of tissue is removed, the appearance and feel of the breast may also be changed. An excisional biopsy is also expensive and has a longer, more painful recovery period.

Incisional Biopsy

Incisional biopsy is a surgical procedure done most often on women with advanced-stage cancer whose tumors are too large to be removed as an initial treatment. Only a portion of the tumor is removed, providing a sufficient amount of tissue to procure information essential for developing a treatment plan.

Breast Cancer

PROGNOSTIC AND PREDICTIVE FACTORS

- Axillary Lymph Nodes
- The Sentinel Node Biopsy
- Tumor Size and Lymph Node Status
- Tumor Grade
- Hormone Receptors
- HER2 Gene Overexpression
- p53 Gene Mutation
- ras Mutation
- BRCA1 and BRCA2 Mutations
- Aggressive Tumors
- Staging

Once cancer is diagnosed, there are several tests performed on lymph node or tumor tissue that can be useful in determining a woman's prognosis and for assessing the type of treatment that will be most effective for her specific breast cancer. The issue of which factors are the most reliable at determining a woman's prognosis and predicting her outcome to certain treatments is perpetually under study. As research progresses, certain factors will fall in and out of favor. Only when found to be accurate and reliable does a factor become a part of standard practice. Commonly assessed prognostic and predictive factors include lymph node status, tumor size, and tumor grade, type of cancer, hormone receptor status, proliferation rate, and HER2/neu (also known as erbB2 expression).

Axillary Lymph Nodes
Lymph nodes are simply small clumps of immune cells acting as filters for the lymphatic system. Like the circulatory system, the lymphatic system runs throughout the body carrying fluid, cells, and other material. When breast cancer spreads, the first places it usually goes is to the axillary lymph nodes in the armpit. The best prognosis is when the cancer remains localized within the breast. Once the cancer spreads beyond the breast, the prognosis worsens.

There are two ways to determine node status. The first method consists of palpating the axillary lymph nodes during a physical examination. If the nodes are enlarged, it is possible that cancer has spread. This method, while fast and convenient, is not very accurate. It has both a 30% false negative and a 30% false positive rate (Harris et al. 1997).

The second method is removal of the nodes from under the armpit in a procedure called an axillary dissection. The nodes are then examined to determine whether or not they contain cancer. This procedure may be performed at different stages of a woman's treatment. However, a standard axillary dissection is typically performed during removal of the breast tumor, and approximately 10-25 lymph nodes are also removed from tissue layers under the armpit.

When an excisional biopsy serves as definitive surgery, the axillary dissection may be performed at the same time or as a separate procedure. Many surgeons now try to perform both procedures together to eliminate the need for separate surgery, anesthesia, and recovery. However, regardless of when the procedure is performed, the node samples are sent to a pathologist for analysis. If the samples do contain cancer, the pathologist will carefully note the number of cancerous nodes and their order and location, from proximal (closest to the breast) to distal (farthest away from the breast).

The Sentinel Node Biopsy
The sentinel node biopsy is a procedure that finds and removes the first (or sentinel) node from the tumor site and examines it to see if it contains cancer cells. If the sentinel node is cancer free, it's likely that the other axillary nodes are cancer free as well (Turner et al. 1997). However, if the sentinel node is positive for cancer, there is a strong likelihood that other nodes may also be involved, and a standard axillary dissection may be required (Weaver et al. 2000).

In order to locate the sentinel node, a colored dye and/or radioactive-labeled tracer is injected into the breast near the tumor. A device called a scintillation counter determines which lymph node is the first node to take up the dye or tracer. This node is then surgically removed and sent to a pathologist for examination.

The advantages of this procedure are that, when done correctly, it is accurate, less traumatic, and it allows axillary dissections to

be done on only those women whose sentinel nodes present positive for cancer.

The disadvantages of the procedure are that it is fairly new, not widely available, and its accuracy depends in large part on the training of the surgeon doing the procedure (Haigh et al. 2000). Several ongoing clinical trials will ultimately determine whether sentinel node biopsy becomes part of the standard diagnostic procedure for breast cancer (Barnwell et al. 1998; Krag et al. 1998; McNeil 1998; Haigh et al. 2000). However, the integration of sentinel node biopsy into contemporary clinical practice is underway (Schwartz et al. 2001).

Tumor Size and Lymph Node Status

Based on numerous studies, there appears to be a strong correlation between tumor size and lymph node involvement. Research demonstrates that the larger the breast tumor, the more likely it is that the lymph nodes will be positive for cancer (Carter et al. 1989). One study of 644 women with tumors 2 cm or smaller found that only 11% of the women with tumors 0.1-0.5 cm in size had axillary lymph node involvement. However, when tumors 1.7-2.0 cm were found, more than 40% of the women had axillary lymph node involvement. The prognosis for breast cancer is related to the size of the tumor. Tumor size can be determined by touch during a physical examination, through imaging with an ultrasound or mammography, or most accurately through post-surgical examination of the tumor. In general, the larger the tumor size, the poorer the prognosis.

Tumor Grade

The grade of a tumor is used to determine how fast a cancer may spread to the lymph nodes or other areas of the body. A pathologist microscopically examines biopsied tissue, determining how closely the cancer cells resemble normal tissue. The less the tumor cells resemble normal tissue, the higher the tumor grade. The pathologist will also assess the rate of cancer cell division. Rapidly dividing cells indicate accelerated tumor growth and therefore a higher tumor grade. Tumor grades are determined as Grade I, or low; Grade II, or medium; and Grade III, or high. Tumor grade is considered directly related to prognosis: the higher the grade, the poorer the prognosis.

Hormone Receptors

An important aspect in any reproductive cancer is whether the tumor growth is hormonally driven. Often breast tumors require hormones for growth, i.e., hormonally responsive tumor. The hormones attach to their receptor sites and promote cell proliferation. Hormone receptor-positive tumors consist of cancer cells with receptor sites for estrogen, progesterone, or both. The receptor status of a tumor is determined by testing tissue removed during a biopsy. Breast cancer can be categorized by its receptor status, which can be estrogen receptor-positive (ER+), estrogen receptor-negative (ER -), progesterone receptor-positive (PR+), progesterone receptor-negative (PR-) or any combination thereof. Both estrogen and progesterone are naturally occurring hormones that the body produces in varying amounts throughout one's lifetime. These hormones are essential for many other physiological functions, such as bone integrity, which will be discussed later in this protocol.

Treatment to block the hormones from attaching to the tumor receptor sites may slow or stop the cancer's growth. The drug most often used in this type of treatment is tamoxifen, which is very effective against receptor-positive cancers. Tamoxifen will be discussed extensively later in this protocol.

HER2 Gene Overexpression

HER2 (human epidermal growth factor receptor 2) is a gene found in every cell of the human body, and its purpose is to help a cell divide. The HER2 gene tells a cell to form the HER2 protein on the cell surface. HER2 protein then receives a signal to send a message to the center of the cell, known as the nucleus, that it is time to divide. The HER2 protein is also called the HER2 receptor.

Each healthy breast cell contains two copies of the HER2 gene, which contribute to normal cell function. When a change occurs that causes too many copies of the HER2 gene to appear in a cell, the gene, in turn, causes too many HER2 proteins, or receptors, to appear on the cell surface. This is referred to as HER2 protein overexpression. Patients who are considered HER2-positive have cancer that grows and spreads more rapidly.

HER2 protein overexpression affects about 25% of breast cancer patients and results in a more aggressive form of the disease and earlier disease reappearance; in these cases the disease may not be as responsive to standard therapies. The HER2 status of a tumor is determined by testing tissue removed during a biopsy.

Herceptin may be considered by breast cancer patients whose tumors over-express the HER2 gene (Nihira 2003).

p53 Gene Mutation

The p53 protein is a tumor suppressor encoded by the p53 gene, whose mutation is associated with approximately 50-60% of human cancers. The p53 gene acts as the guardian of DNA and, in the event of DNA damage, it performs several crucial functions. The p53 gene acts as a checkpoint in the cell cycle inducing growth arrest (halting the cell cycle) by increasing the expression of the p21 gene. It initiates DNA repair. If the DNA can be repaired, the p53 gene prevents apoptosis (programmed cell death), or if the DNA cannot be repaired, it initiates apoptosis. The p53 protein also plays a role in the transcription ("reading") of DNA by binding to and initiating the expression of multiple genes.

When a mutation in the p53 gene occurs, one amino acid is substituted for another and p53 loses its ability to block abnormal cell growth. Indeed, some mutations produce a p53 molecule that actually stimulates cell division and promotes cancer. These cancers are more aggressive, more apt to metastasize, and more often fatal.

People inheriting only one functional copy of the p53 gene from their parents are predisposed to cancer in early adulthood. Usually several independent tumors develop in a variety of tissues. This is a rare condition known as Li-Fraumeni syndrome. The p53 gene has been mapped to chromosome 17p13, and mutations in the p53 gene are found in most tumor types and contribute to the molecular events that lead to tumor formation.

Since the hallmark of cancer is the unchecked proliferation of cells, the role of p53 is critical. The question then becomes, if the p53 gene is a built-in tumor suppressor, why does cancer still develop? The answer is that the p53 molecule can be inactivated in several ways. As discussed earlier, in some families p53 mutations are inherited and family members have a high incidence of cancer. More often, the p53 molecule is inactivated by an outside source.

In the cell, p53 protein binds DNA, which in turn stimulates another gene to produce a protein called p21 that interacts with a cell division-stimulating protein (cdk2). When p21 binds with cdk2, the cell cannot pass through to the next stage of cell division. Mutant p53 can no longer bind DNA in an effective way, and as a consequence the p21 protein is not made available to act as the "stop signal" for cell division. Thus, cells divide uncontrollably and form tumors. DNA tumor viruses, such as the human adenovirus and the human papilloma virus can bind to and inactivate the p53 protein function, altering cells and initiating tumor growth. In addition, some sarcomas amplify another gene, called mdm-2, which produces a protein that binds to p53 and inactivates it, much the way the DNA tumor viruses do.

The amount of information that exists on all aspects of p53 normal function and mutant expression in human cancers is vast, reflecting its key role in the pathogenesis of human cancers. It is clear that p53 is just one component of a network of events that culminate in tumor formation.

ras Mutation

The ras oncogenes often governs the regulation of cancer cell growth. The ras family is responsible for modulating the regulatory signals (mitogen activated protein kinase (MAPK) signal transduction cascade) that govern the cancer cell cycle and proliferation. The Ras protein also plays a role in initiating a number of other signal transduction cascades, including phosphoinositide (PI) kinase, and the activation of protein kinase C (PKC). Inhibition of Ras protein action is important because ras induces the expression of the MDM2 gene, whose protein serves to inhibit the activity of the p53 protein. In this way, ras activity reduces the ability of the p53 protein to induce cell death (apoptosis) in cancer cells. Mutations in genes encoding ras proteins have been intimately associated with unregulated cell proliferation of cancer. Further, since ras protein plays an important role in multiple signal transduction pathways and is overexpressed in a large number of cancers, the inhibition of ras is now considered a goal in cancer treatment (Rowinsky et el. 1999).

BRCA1 and BRCA2 Mutations

BRCA1 and BRCA2 are familial (inherited) gene mutations that have been linked to breast cancer. BRCA1 is a tumor suppressor gene located on the long arm of chromosome 17, and BRCA2 is located on chromosome 13. Tumor suppressor genes play a role in regulating cell growth. When one copy of BRCA1 is inherited in a defective (mutant) form, a woman is predisposed to breast and ovarian cancer. However, BRCA1 mutations do not appear critical for the development of the majority of breast and ovarian cancers. Development of cancer in either organ involves a number of additional mutations, at least one of which involves the other copy (allele) of BRCA1. A woman who inherits one mutant allele of BRCA1 from either her mother or father has a greater than 80% risk of developing breast cancer during her life. While it appears that a high number of currently identified high-risk families have mutations in either the BRCA1 or BRCA2 genes, hereditary breast cancer accounts for only about 5% of all cases of breast cancer.

Testing tumors in women with breast cancer for the BRCA1 gene could increase the effectiveness of chemotherapy dramatically. Cancer cells with functional BRCA1 are highly resistant to one type of chemotherapy but extremely sensitive to another. In laboratory tests tumor cells react differently to anti-cancer agents depending on the BRCA1 gene activity. A functioning BRCA1 gene made tumor cells more than 1,000 times more sensitive to drugs such as Taxol and Taxotere, which work by blocking the final stage of cell division. The same cells, however, were between 10 and 1,000 times more resistant to drugs like cisplatin that

work by damaging DNA within tumors. Assessing a tumor's BRCA1 status may be invaluable in deciding which type of chemotherapy to use.

The BRCA1 gene plays an important role in stopping the development of cancer, and women who inherit a damaged version of this gene have a high risk of developing breast cancer. BRCA1 may also get "switched off" in as many as 30 percent of tumors, even in patients who inherit a normal version of the gene.

Aggressive Tumors

Certain tumors may be classified as aggressive based on a number of prognostic factors, such as tumor type, size, and grade. Typically, an aggressive tumor is one that under microscopic examination shows signs of fast growth and has a high grade. Because aggressive tumors have a greater chance of spreading to other areas of the body and returning after treatment, they are often treated more intensively. One example of an aggressive tumor is inflammatory breast cancer.

Staging

Cancer is classified into stages, which determine treatment and prognosis. There are a number of methods for staging breast cancer. The most widely used is the TNM classification (Tumor, Nodes, Metastases). TNM takes into account the size of the tumor (T), the number of cancerous lymph nodes (N), and whether or not the cancer has spread to other areas of the body (metastasis) (M). The stage of cancer is usually determined twice. The first is clinical staging, which is based on results from a physician's physical exam and tests such as mammography. The second is pathologic staging based on a direct examination of the lymph nodes and a tumor removed during surgery.

Tumor Size

TX:	Tumor size cannot be assessed
T0:	No tumor can be found
Tis:	Only carcinoma in situ
T1:	Tumor is 2 cm or smaller

Subcategories of T1:

T1mic:	Very small tumor (0.1 cm or smaller)
T1a:	Tumor is larger than 0.1 cm, but no larger than 0.5 cm
T1b:	Tumor is larger than 0.5 cm, but no larger than 1 cm
T1c:	Tumor is larger than 1 cm, but no larger than 2 cm

T2	Tumor is larger than 2 cm, but no larger than 5 cm
T3	Tumor is larger than 5 cm
T4	Tumor is any size, but has expanded past the breast tissue to the chest wall or skin

Subcategories of T4:

T4a:	Tumor has expanded to chest wall
T4b:	Tumor has expanded to skin
T4c:	Tumor has expanded to both chest wall and skin
T4d:	Presence of inflammatory carcinoma

Lymph Node Status

NX:	Nodes cannot be evaluated. This can happen if, for example, they have been removed previously.
N0:	Axillary nodes do not have cancer
N1:	Axillary nodes have cancer, but can be moved
N2:	Axillary nodes have cancer and are fixed to each other or the chest wall (cannot be moved)
N3:	Internal mammary nodes have cancer

Distant Metastases

MX:	Distant metastases cannot be assessed
M0:	No distant metastases
M1:	Distant metastases

In Situ Cancer

Stage 0:	TisN0M0

Early Stage Invasive Cancer

Stage 1:	T1N0M0
Stage 2a*	T0N1M0
	T1N1M0
	T2N0M0
Stage 2b*	T2N1M0
	T3N0M0

Advanced Stage Invasive Cancer

Stage 3a:	T0N2M0
	T1N2M0
	T2N2M0
	T3N1M0
	T3N2M0
Stage 3b:	T4, any N, M0
	Any T, N3, M0

Metastatic Breast Cancer

Stage 4:	Any T, any N, M1

**Though classified here as "early stage," prognosis can be poor for some
stage 2 cancers, particularly those with multiple lymph node involvement.*

Breast Cancer

TESTS FOR DISTANT METASTASES

Cancer cells have the ability to leave the original tumor site, travel to distant locations, and metastasize in organs such as the liver, lungs, or bones. The process of metastasis is dynamic and requires an optimal environment in order for a tumor cell to proliferate, invade surrounding tissues, be released into the circulation, adhere to blood vessels in the liver, invade the liver, proliferate, and establish its own blood supply (tumor angiogenesis). This complex process requires interaction of tumor cells with the microenvironment of the liver to the extent that the tumor cell can utilize the growth factors and blood vessels of the liver in order to grow.

In addition to tests for prognostic and predictive factors, women diagnosed with node-positive breast cancer will require a number of tests to confirm that the cancer has not spread to other organs, such as the lungs, liver, and bone. Only about 6% of women when first diagnosed with breast cancer have distant metastases (Ries et al. 2000). Most women found to have metastases have previously been treated for the disease and are experiencing a recurrence.

Symptoms such as shortness of breath, a chronic cough, weight loss, and bone pain may indicate distant metastases. However, only after specific tests can the occurrence of distant metastasis be confirmed or ruled out. The three primary tests performed are blood tests that check for liver and/or bones metastasis, bone scans to test for bone metastasis, and x-ray/CT scans to test for chest, abdomen, and liver metastasis. Based on the results of the primary tests and the symptoms the woman experiences, further testing may be required.

Common Tests for Distant Metastases

1. **X-rays**. An x-ray is a test in which an image is created using low doses of radiation reflected on film paper or fluorescent screens providing an image of specific areas. The films created by x-rays show different features of the body in various shades of gray. The darkest images are those areas that do not absorb x-rays well; the lighter images are dense areas (like bones) that absorb more of the x-rays. To enhance visibility, some x-ray exams will use a contrasting solution that can be swallowed, injected intravenously into the circulatory system, or given by an enema to locate or confirm possible metastases.
2. **Computer Axial Tomography (CAT or CT) scan**. This procedure combines the use of a digital computer together with a rotating x-ray device to create detailed cross-sectional images, or "slices," of the different organs and body parts. This procedure may or may not involve injecting an intravenous contrasting solution into the circulatory system. It does, however, always involve exposure to ionizing radiation. A CAT scan has the unique ability to image a combination of soft tissue, bone, and blood vessels and can assist in locating possible metastasis.
3. **Magnetic Resonance Imaging (MRI)**. MRIs involve no ionizing radiation and can be used for precise imaging of any organ suspected of having metastases. This is a special imaging technique used to image internal structures of the body, particularly the soft tissues. An MRI image is often superior to a normal x-ray image. In an MRI exam, the patient passes through a tunnel surrounded by a magnet, which polarizes hydrogen atoms in the tissues and then monitors the summation of the energies within living cells. A computer tracks the magnetism and produces a clear picture of the tissues, particularly soft tissues. Images are very clear and are particularly good for soft tissue, brain, and spinal cord, joints, and abdomen. These scans may be used for detecting some cancers or for following their progress.
4. **Positron Emission Tomography (PET)**. A highly specialized imaging technique using short lived substances such as simple sugars (glucose), which are labeled with signal emitting tracers (18-fluoro-deoxyglucose (18-FDG)) and injected into the patient. A scanner records the signals these tracers emit as they travel through the body and collect in various organs targeted for examination. Although all cells use glucose, more glucose is used by cells with increased metabolism such as tumor cells, which use more glucose than neighboring cells, and thus, they are easily seen on the PET scan. PET uses a camera that produces powerful images to reveal metastasis that other imaging techniques simply cannot detect. This technique is very sensitive in deciphering and picking up active cancer cells or tumor tissue but does not measure size. PET can follow the course of cancer through the body and accurately show the extent of the disease. PET can differentiate between normal tissue, scar tissue, and malignant cancerous tissue.
5. **Ultrasound.** Very high frequency sound waves are used to produce an image of many of the internal structures in the body without exposure to ionizing radiation. This is highly operator-dependent and is thought to be useful in diagnosis but not particularly accurate in the assessment of tumor response. For the latter, CT or MRI scans are more accurate. Intraoperative ultrasonography is useful in the detection of liver metastases.
6. **Bone Scan**. A bone scan is a nuclear medicine study of the body skeleton used to look for cancer, stress fractures, and other bone or joint problems. It does not measure bone density and is not used to diagnose osteoporosis. This procedure uses a radioisotope tracer (Technetium-99m MDP or HDP) injected intravenously into the circulatory system. This radioactive compound localizes in the bone and the distribution of the radioactivity in the body is recorded by the radionuclide scanner (better known as a gamma or scintillation camera), producing an image of the tracer's distribution in the skeletal system. This recording can reveal the presence of bone metastases.

7. **Bone Density.** Since excessive bone breakdown releases tumor growth factors into the bloodstream that can fuel cancer growth, a bone density scan and a test that can be used to assess bone resorption rates should be regularly performed for cancer patients. All bone density scan measurements with the exception of ultrasound use small doses of radiation to determine the amount of bone present.

8. **DPD.** The deoxypyridinoline (DPD) cross-links urine test (Pyrilinks-D) can be used to assess bone resorption rates; this test should be done every 60-90 days to detect bone loss in patients with cancer that has a proclivity to spread to bone. A QCT bone density scan should be done annually. Every cancer patient should take a bone-protecting supplement to protect against excess bone breakdown. For information regarding maintaining bone integrity refer to the protocol Cancer Treatment: The Critical Factors.

9. **QCT. Quantitative Computed Tomography,** or QCT Densitometry (often referred to as a QCT bone density scan) is a method used to measure bone mass. The principle underlying QCT densitometry and other bone mass measurements (such as DXA) is that calcified tissue will absorb more x-rays than surrounding tissue so that the CT density measurement can be used to measure total bone mass within a sample of tissue. With proper technique, precision for the conventional (2D) method is 2-3%, and about 1% for 3D QCT, so monitoring patients at yearly intervals yields clinically useful results. Only QCT isolates the metabolically active bone for analysis. The QCT examination is performed on any modern CT scanner and takes approximately 10 minutes. Insurance companies and Medicare may reimburse for QCT examinations.

10. **DXA**. DXA stands for dual x-ray absorptiometry. It was previously known as DEXA, dual energy x-ray absorptiometry. Low dose x-rays of two different energies are used to distinguish between bone and soft tissue, giving an accurate measurement of bone density at these sites. However, DXA also includes aortic calcification and osteophytes in the calculation of bone mineral. Lateral DXA, has been shown to have a sensitivity intermediate between the high sensitivity of QCT and the somewhat lower one of conventional DXA (used for detection of osteoporosis), but it uses 4-10 times the radiation exposure, is less precise, and the study time is increased compared to conventional DXA/QDR.

11. **Blood Tests**. A variety of blood tests can assess the health of different organs and systems in your body. "Cancer marker" tests can detect possible cancer activity in the body. If cancer is present, it can produce specific protein in the blood that can serve as a "marker" for the cancer. CA 15.3 is the name of a protein used to find breast and ovarian cancers, although it is important to note that there may be insufficient quantities of this protein present in the blood to ensure early stage breast cancer detection. Creatine-kinase-BB serves as a marker for breast, ovarian, colon, and prostate cancers. CEA (carcinoembryonic antigen) is a marker for the presence of colon, lung, and liver cancers and a marker for secondary breast and ovarian cancer sites. CA125 may signal ovarian cancer and secondary breast and colorectal cancer sites. TRU-QUANT and CA 27.29 are other examples of proteins associated with the recurrence of breast cancer (more information on tumor markers will follow). Blood tests should evaluate for the presence of anemia or hepatic dysfunction, both of which can be consequences of the patient's underlying cancer.

TREATMENT OF BREAST CANCER

- Localized Treatment
- Adjuvant Treatment

In the past 20 years, many strides have been made to improve the treatment of breast cancer. Some of the trauma associated with breast cancer treatment has been reduced because of increased early detection through mammography, surgery options that conserve much of the breast, and the increasing long-term survival rate. The treatment goal is to rid the body of the cancer as completely as possible and to prevent the cancer from returning. This is usually accomplished by utilizing multimodalities, including surgery, anticancer drugs (chemotherapy), irradiation, hormone therapy, nutritional supplementation, and diet modification.

Surgery and radiation therapy are considered local treatments. They focus on eliminating cancer from a limited or local area - such as the breast, chest wall, and axillary nodes. Chemotherapy, hormone therapy, nutritional supplementation, and diet modification are considered systemic therapy. In systemic therapy, the entire body is treated in order to eradicate any cancer cells that may have spread from the breast tumor to other areas of the body.

Treatment depends on many factors, such as age, tumor stage, and estrogen-receptor status. However, deciding on a particular treatment is both a personal and a medical choice. Each treatment option has risks and benefits. Therefore, the type of treatment a woman chooses should be based on an understanding of how these risks and benefits relate to one's personal values and lifestyle.

LOCALIZED TREATMENT

- Surgery
- Radiation Therapy

Surgery

- Breast-Conserving Surgery
- Total Mastectomy
- Luteal Phase Surgery

Breast cancer surgery strives to completely remove the tumor from the breast. However, surgery may also include the removal of one, some, or all of the axillary lymph nodes. Following surgery, both the tumor and/or lymph nodes are sent to a pathologist for examination to determine the stage of the breast cancer so the physician and patient can decide what additional treatment may be required after surgery.

There are two basic types of surgery for breast cancer: breast-conserving surgery and total mastectomy.

Breast-Conserving Surgery

Breast-conserving surgery consists of the removal of the breast tumor and some surrounding normal tissue. This procedure can be referred to as a lumpectomy, wide excision, or partial-radical mastectomy. During the operation, axillary lymph nodes may also be removed.

During breast-conserving surgery, the patient is usually given general anesthetic, causing unconsciousness. The surgeon then opens the breast and removes the tumor and a small amount of normal tissue. The surgeon then sutures together the edges of the incision, trying to keep the breast as normal looking as possible.

If axillary lymph nodes are removed, the surgeon will also open the area under the armpit on the same side as the affected breast, removing about 10-15 lymph nodes. However, if a sentinel node biopsy is performed only 1-3 lymph nodes are removed and used to assess node status.

Breast-conserving surgery can be done on palpable tumors (tumors that the physician is able to feel), as well as tumors that are not palpable but that can be located by mammography. In the case of tumors that are not palpable, a radiologist will insert a very thin wire into the area of the tumor in the breast during a mammogram. This procedure is called wire-localization or needle-localization (and was discussed earlier). The wire remains in the breast until the surgery and serves as a guide for the surgeon.

The tumor and lymph nodes removed during surgery are sent to a pathologist, who will assess the tumor margins to determine whether there is an adequate amount of normal tissue surrounding the tumor. This margin of normal tissue helps indicate whether or not the entire tumor was removed. If clean, uninvolved, or negative margins are found, this indicates that only normal tissue remains at the edges of the tissue removed and no additional surgery is needed. If normal tissue does not completely surround the tumor, the margins are considered "dirty," "involved," or "positive." Additional surgery will then be done to obtain adequate margins (Love et al. 1997).

A second breast-conserving operation is usually done if the tumor margins are found to be "dirty." This surgery is called a re-excision. If it does not achieve negative margins, a total mastectomy may be recommended.

Total Mastectomy

A total mastectomy procedure entails the removal of the entire breast. This may include an axillary dissection as well. For women who have decided to have breast reconstruction, this procedure will directly follow the mastectomy surgery.

A total mastectomy is done under general anesthetic. During the operation, all of the breast tissue is removed, including the nipple. For women considering breast reconstruction during or sometime after surgery, as much skin as possible is left intact in order to cover the implant. If a woman is not having reconstruction or is having it at a later time, the skin in the area is sewn together and a drainage tube is inserted so fluid from the healing wound can drain away.

The pathologist will evaluate the breast tissue and lymph nodes. The results of these tests will help determine which adjuvant therapy will be used.

Luteal Phase Surgery

Studies have suggested that premenopausal women who have their breast-conserving procedure or mastectomy done during the later part of their menstrual cycle (during the luteal phase) may have a better outcome after surgery. However, researchers are still assessing the benefits to "timing surgery" (Senie et al. 1997; NCI 1998).

Radiation Therapy

Radiation therapy (also known as radiotherapy) is considered a local treatment for breast cancer that uses targeted, high-energy x-rays to impede cancer cells' ability to grow and divide. The aim of radiation therapy is to rid the breast, chest, and axillary lymph nodes of cancer by using high-energy x-rays. For women with early-stage breast cancer, radiation therapy is most often performed following breast-conserving surgery. It is believed that after conserving surgery, there may still be microscopic cancer in the breast undetectable to the naked eye. Therefore, to reduce the chance of recurrence, radiation therapy is necessary to eliminate any remaining cancer.

Radiation therapy may also be used on the axillary lymph nodes and the chest wall following total mastectomy. Radiation therapy usually commences several weeks after surgery. However, it may be postponed if a patient is receiving chemotherapy first. (For more information regarding radiation therapy, please see the Cancer Radiation Therapy protocol.)

Breast Cancer

ADJUVANT TREATMENT

- Chemotherapy
- Hormone Therapy
- Natural Therapy

The goal of an adjuvant treatment is to systemically eliminate any cancer cells or micrometastases that may have spread from the breast tumor to other parts of the body as well as to eliminate any microscopic cancer cells that may remain in the local breast/lymph node area. These therapies are referred to as adjuvant, meaning "in addition to," because they are used with surgery and radiation. It is called adjuvant systemic therapy because the entire system of the body is treated. Several types of adjuvant systemic treatments are used for early-stage breast cancer: chemotherapy and hormone therapy are well established conventional adjuvant therapies; nutritional supplementation and diet modification may be incorporated in any conventional adjuvant treatment plan.

Except for some women with very small tumors (less than 1 cm) and with lymph nodes that do not have cancer, adjuvant therapy is usually recommended for women with early-stage breast cancer. Which therapies, and in what combination, depends on many things, such as the woman's age, whether the tumor has estrogen receptors, and the number of positive lymph nodes.

Chemotherapy

Chemotherapy uses drugs that can be taken in oral form or injected intravenously to kill cancer cells; sometimes, a combination is used. However, intravenous drugs are usually given in a hospital or doctor's office. Depending on the drugs used, chemotherapy is administered once or twice a month for 3-6 months. Sometimes the range might be extended to 7 or 8 months. Chemotherapy usually begins 4-6 weeks after the final surgery and is administered in a combination of 2-3 drugs that have been found to be the most effective. Unfortunately, chemotherapy drugs have many side effects that can damage or destroy normal healthy tissues throughout the body.

Although the exact schedule depends on the specific drugs used, drugs may be given on day 1 of a 3-week cycle or there may be a period of a week or two on the drugs, followed by a period of about 2 weeks off the drugs. This cycling allows the body a chance to rest and recover between treatments; however, it also gives the cancer cells an opportunity to rest, recover, and possibly mutate into a type of cancer that is chemotherapy-resistant. An entire course of chemotherapy lasts about 4-6 months, depending on the drugs used. Recent studies indicate that a more efficacious approach would be to lower the dose of conventional chemotherapy agents, reschedule their application, and combine them with agents designed to interfere with cancer's ability to produce new blood vessels (anti-angiogenic agents) (Holland et al. 2000).

This lower-dose approach, known as "metronomic dosing," uses a dosing schedule as often as every day. An amount as low as 25% of the maximum tolerated dose (MTD) in combination with anti-angiogenesis agents targets the tumor endothelial cells making up the blood vessels and microvessels feeding the tumor. Tumor endothelial cells can be killed with much less chemotherapy than tumor cells, and the side effects to healthy tissue and the patient in general are dramatically reduced (Hanahan et al. 2000).

While chemotherapy is an effective treatment for many women, it is associated with a number of well-known and traumatic side effects, such as hair loss, and exhausting bouts of nausea and vomiting, which many patients find difficult to tolerate. (For more information on chemotherapy, please refer to the Cancer Chemotherapy protocol.)

Hormone Therapy

- Tamoxifen
- Raloxifene
- Toremifene
- Anastrozole, Femara, Aromasin
- Megestrol Acetate
- Trastuzumab
- Paclitaxel
- Oophorectomy

Breast tumors often require hormones for growth, which poses a unique problem because the hormones involved in tumor growth are either estrogen, progesterone, or both. Estrogen and progesterone are naturally occurring and necessary hormones, produced mainly in the ovaries and adrenal glands in varying amounts throughout a woman's lifetime. These hormones are essential for many physiological functions, such as bone integrity, which will be discussed later in this protocol.

Hormone receptor-positive tumors can consist of cancer cells with receptor sites for estrogen, progesterone, or both. The hormones attach to receptor sites and promote cell proliferation. Hormone therapy blocks the hormones from attaching to the tumor receptor sites and may slow or stop the cancer's growth. The drug most often used in this type of endocrine therapy is tamoxifen, with a response rate from 30-60%. Other therapies are sometimes used, such as aromatase inhibitors (that inhibit the conversion of precursors to estrogens) or oophorectomy (the removal of the ovaries).

The effective role of some newer hormonal therapies in the treatment of both pre- and post-menopausal women with early breast cancer has been studied. Hormonal therapy with goserelin, either with or without tamoxifen, has been endorsed as an alternative to chemotherapy for young women with hormone-sensitive disease since it is equally effective and better tolerated. Twenty-five percent of all women diagnosed with breast cancer are premenopausal; of these women approximately 60% have hormone-sensitive tumors.

While chemotherapy kills cancer cells by destroying all rapidly dividing cells in the body, goserelin suppresses the supply of estrogen from the ovaries, which stimulates the cancer cells to grow. This is achieved by inhibiting production of another hormone called luteinizing hormone (LH), which stimulates the ovaries to make estrogen. Since many breast cancers grow more rapidly in the presence of estrogen, this can help to reduce tumor growth.

Tamoxifen prevents estrogen from stimulating cancer cell growth by blocking the estrogen receptors in the cancer cells. Cutting off the cancer's supply of estrogen provides an effective alternative method of combating the disease and avoids the distressing side effects of chemotherapy. Based upon evidence from adjuvant studies, hormonal therapy with goserelin is better-tolerated and equally effective as an alternative to chemotherapy. This gives physicians and patients a real choice in treatment following initial surgery (Goldhirsch et al. 2003).

Tamoxifen (Nolvadex)

Tamoxifen is an anti-estrogenic drug used to treat women whose tumors are estrogen or progesterone receptor-positive. This endocrine therapy blocks the female hormone estrogen from binding to the tumor cells. Tamoxifen has been the gold standard hormonal agent used for the treatment of breast cancer for more than 8 years. It is a prototype for a class of compounds called selective estrogen receptor-modulators (SERMs) of breast cancer but is also an effective primary treatment for advanced disease. Women with early-stage breast cancer who take tamoxifen have, on average, a 25% proportional increase in their chances of surviving 5 years after diagnosis.

Tamoxifen does not work equally well in all women. As the name implies, estrogen receptor-negative tumors do not have estrogen receptors, and therefore do not respond to tamoxifen. A Phase III study of 2691 high-risk cancer patients tested the effectiveness of tamoxifen with both pre- and postmenopausal subsets of receptor-negative and receptor-positive tumors. Both the 5-year disease-free and overall survival in patients with receptor-positive tumors treated with the addition of tamoxifen to chemotherapy was significantly higher than with chemotherapy alone, while no such advantage in disease-free or overall survival was found in receptor-negative patients. Further, in the receptor-positive postmenopausal group, the addition of tamoxifen showed a significant improvement in both disease-free and overall survival. However, in the premenopausal receptor-negative patients, tamoxifen led to a worse outcome, as indicated by the significantly reduced survival rate (ONI 2000). Women with estrogen receptor-negative tumors may receive chemotherapy instead of tamoxifen.

Therefore, for the patient whose breast cancer's growth is estrogen-dependent, tamoxifen can keep estrogen from these cells, slowing or stopping their growth. Tamoxifen is a pill taken daily for 5 years. To date, studies do not show any benefit to taking tamoxifen for longer than 5 years (NCI 1998). Studies show that the use of tamoxifen as a post-surgical adjuvant therapy can reduce the chances of the cancer reoccurring.

Tamoxifen has a host of side effects, including hot flashes, weight gain, mood swings, abnormal secretions from the vagina, fatigue, nausea, depression, loss of libido, headache, swelling of the limbs, decreased number of platelets, vaginal bleeding, blood clots in the large veins (deep venous thrombosis), blood clots in the lungs (pulmonary emboli), cataracts (Fisher et al. 1998), and--the side effect of the greatest concern--endometrial cancer (Harris et al. 1997).

Studies have shown an increase of early-stage endometrial cancer (cancer of the lining of the uterus) among women taking tamoxifen, and the risk increases if the drug is taken for more than 5 years. Endometrial cancer is usually diagnosed at a very early stage and is usually curable by surgery. The studies have also shown an increased risk of uterine sarcoma (a rare cancer of the connective tissues of the uterus) among women taking tamoxifen. Unusual vaginal bleeding is a common symptom of both of these cancers. The treating physician should be notified immediately if vaginal bleeding occurs.

Raloxifene

Raloxifene is a drug similar to tamoxifen. It is a selective estrogen receptor-modulator (SERM) that blocks the effect of estrogen on breast tissue and breast cancer. It is currently in the testing phase to assess its effectiveness in reducing the risk of developing breast cancer. Pending testing completion, this drug is not recommended as hormonal therapy for women who have been diagnosed with breast cancer.

Toremifene (Fareston)

Toremifene (Fareston) is an anti-estrogen drug closely related to tamoxifen that may be an option for postmenopausal women with breast cancer that has metastasized. Fareston is a type of anti-estrogen medication that is used in tumors that are estrogen-receptor-positive or estrogen receptor-unknown.

Some patients treated with anti-estrogens who have bone metastasis may experience a tumor flare with pain and inflammation in the muscles and bones that will usually subside quickly. Blood calcium level should be monitored because tumor flare can cause a raised level of calcium in the blood (hypercalcemia) with symptoms of nausea, vomiting, and thirst. Often a short stay in the hospital is necessary until the calcium levels have been reduced or treatment may need to be stopped. Fareston is being studied in clinical trials for use in earlier stages of breast cancer.

Anastrozole (Arimidex), Femara (Letrozole), and Aromasin (Exemestane)

Anastrozole (Arimidex), Femara (Letrozole), and Aromasin (Exemestane) are three hormonal therapy drugs referred to as aromatase inhibitors. Aromatase is the enzyme that converts male hormones (testosterone) into female hormones (estrogens) in postmenopausal women. Premenopausal women get most of their estrogen from the ovaries. But postmenopausal women still have estrogen in their bodies, and it is this conversion to estrogen of androgens coming from adrenal glands in the body that needs to be interrupted so the breast cancer cells no longer have estrogen to stimulate their growth. Unlike tamoxifen, which slows the growth of breast cancer by preventing estrogen from activating its receptor, anastrozole blocks an enzyme needed for the production of estrogen, inhibiting the conversion of precursors to estrogens, and is effective in hormone receptor-positive breast cancers. Anastrozole is currently an option for women whose advanced breast cancer continues to grow during or after tamoxifen treatment.

Studies are ongoing to compare tamoxifen and anastrozole as adjuvant hormonal therapies. Anastrozole (Arimidex) was better than tamoxifen at preventing the recurrence of breast cancer in a study conducted in 381 centers in 21 countries, involving 9366 patients, and examining three treatment arms: tamoxifen alone, tamoxifen in combination with other therapy, and anastrozole alone. The trial results showed that women taking anastrozole experienced fewer side effects than women taking tamoxifen. However, women taking tamoxifen experienced fewer musculoskeletal disorders. The study was only conducted for a relatively short period of time, 2 years, and the long-term effects (5 years and beyond) are not yet known. Longer-term studies are needed to assess both the benefits and risks of this therapy. However, most recent studies have showed anastrozole to be slightly superior to tamoxifen (Susman 2001).

In a primary trial of 33 months, anastrozole was superior to tamoxifen in terms of disease-free survival (DFS), time to recurrence (TTR), and incidence of contra-lateral breast cancer (CLBC) in adjuvant endocrine therapy for postmenopausal patients with early-stage breast cancer. After an additional follow-up period of 47 months, anastrozole continued to show superior efficacy.

When compared with tamoxifen, anastrozole has numerous advantages in terms of tolerability. Endometrial cancer, vaginal bleeding and discharge, cerebrovascular events, venous thromboembolic events, and hot flashes all occurred less frequently in the anastrozole group. However, musculoskeletal disorders and fractures continued to occur less frequently in the tamoxifen group. The study concluded that the benefits of anastrozole are likely to be maintained in the long term and provide further support for the status of anastrozole as a valid treatment option for postmenopausal women with hormone-sensitive early-stage breast cancer (Baum 2003).

The biological basis for the superior efficacy of neoadjuvant letrozole versus tamoxifen for postmenopausal women with estrogen receptor (ER)-positive locally advanced breast cancer was investigated. Letrozole inhibited tumor proliferation more than tamoxifen. While the molecular basis for this advantage was complex, it appeared to include a possible tamoxifen agonist effect on the cell cycle in both HER1/2+ and HER1/2- tumors. Letrozole seems to inhibit tumor proliferation more effectively than tamoxifen independent of HER1/2 expression status (Ellis et al. 2003).

Letrozole (2.5 mg per day) and anastrozole (1 mg per day) were compared as endocrine therapy in postmenopausal women with advanced breast cancer previously treated with an anti-estrogen. Letrozole was significantly superior to anastrozole in the overall response rate (ORR) and both agents were well tolerated. Advanced breast cancer is more responsive to letrozole than anastrozole as a second-line endocrine therapy, as letrozole has the greater aromatase-inhibiting activity (Rose et al. 2003). These results

support previous studies which showed that letrozole (Femara) was significantly more potent than anastrozole (Arimidex) in inhibiting aromatase activity in vitro and in inhibiting total body aromatization in patients with breast cancer.

A once a day oral dose of Femara lowered the risk of breast cancer recurrence by 43% in 5000 older women who had already completed 5 years of treatment with tamoxifen. After just over 2 years, 207 women had a recurrence of cancer - 75 in the Femara group and 132 in the placebo group. There were 31 deaths in women receiving Femara and 42 deaths in women receiving placebo. Compared with placebo, Femara therapy after the completion of standard tamoxifen treatment significantly improved disease-free survival. This is a significant finding because in more than 50% of women treated for breast cancer, the cancer recurs 5 or more years after the original diagnosis (Goss et al. 2003).

Possible side effects of aromatase-inhibitor drugs include those associated with menopausal-like estrogen deficiency, such as hot flashes, night sweats, menstrual irregularity, depression, bone or tumor pain, pulmonary embolism (a blood clot in the lung), musculoskeletal disorders, and generalized weakness.

Megestrol Acetate
Megestrol acetate (Megace) is another drug used for hormonal treatment of advanced breast cancer, usually for women whose cancers do not respond to tamoxifen or have stopped responding to tamoxifen. Megestrol acetate is a man-made substance called progestin that is similar to the female hormone progesterone.

As with other therapies, there are reported side effects, including an increase in appetite causing weight gain, fluid retention causing ankle swelling, and nausea at the onset of therapy, which usually subsides. In rare cases, allergic reactions, jaundice, and raised blood pressure have been reported.

Breast Cancer

Trastuzumab (Herceptin Genentech)
Trastuzumab (Herceptin Genentech) is an anticancer drug therapy for women with HER2-positive metastatic breast cancer. This monoclonal antibody therapy differs from traditional treatments, such as chemotherapy and hormone-blocking therapy. Herceptin works by specifically targeting tumor cells that overexpress the HER2 protein. A monoclonal antibody blocks the receptors and prevents activation of genes that induce cell division, thereby slowing the growth of the tumor.

The reported side effects are chills, diarrhea, nausea, weakness, headache, vomiting, and possibly damage of the heart muscle, anemia, and nerve pain. Trastuzumab can be used alone or in combination with the drug paclitaxel (Taxol) and is prescribed for metastatic breast cancer.

Paclitaxel (Taxol)
Paclitaxel (Taxol) belongs to the group of medicines called antineoplastics (anticancer drugs) that interfere with the growth of cancer cells and eventually destroy them. Because the growth of normal cells may also be affected by paclitaxel, side effects can occur. Some side effects may not occur until months or years after the medicine was used.

Side effects include neutropenia (decreased white blood cell count), anemia (decreased red blood cell count), thrombocytopenia (decreased platelet count), increased risk of infection, fatigue, bruising, hemorrhage, rash, itching, redness, hives, facial flushing, chest pain, difficulty breathing, high or low blood pressure, decreased heart rate, lightheadedness, dizziness, increased perspiration, shortness of breath, headache, numbness or tingling of the hands and/or feet, muscle aches, bone pain, mouth ulcers (sores), alopecia (loss or thinning of scalp and body hair), decreased appetite, diarrhea, nausea, vomiting, skin burns and ulcers, nail changes, hot flashes, and vaginal dryness.

Oophorectomy
Oophorectomy is surgery in which the ovaries are removed, therefore eliminating the body's main source of estrogen and progesterone in premenopausal women. Prior to the advent of anti-estrogen drugs, an oophorectomy was commonly used to treat breast cancer in premenopausal women.

Occasionally this procedure is still used in premenopausal women. However, chemotherapy drugs can alter the ovaries and reduce estrogen production. Tamoxifen may block any remaining estrogen effect on cancer cells, allowing many women to avoid surgery.

Natural Therapies

- Protecting Against Dangerous Estrogens
- Curcumin
- Green Tea
- Conjugated Linoleic Acid
- Caffeine
- Melatonin
- Se-Methylselenocysteine
- CoQ10
- EPA and DHA
- Vitamins A, D, and E
- Tocotrienols

Protecting Breast Cells Against Dangerous Estrogens

- I3C
- How to Use I3C

The stronger form of estrogen, estradiol, can be converted into the weaker form, estriol, in the body without using drugs. Estriol is considered to be a more desirable form of estrogen. It is less active than estradiol, so when it occupies the estrogen receptor, it blocks estradiol's strong "growth" signals. Using a natural substance the conversion of estradiol to estriol increased by 50% in 12

healthy people (Michnovicz et al. 1991). Furthermore, in female mice prone to developing breast cancer the natural substance reduced the incidence of cancer and the number of tumors significantly. The natural substance was indole-3-carbinol (I3C).

Indole-3-carbinol (I3C) is a phytochemical isolated from cruciferous vegetables (broccoli, cauliflower, Brussels sprouts, turnips, kale, green cabbage, mustard seed, etc.). I3C given to 17 men and women for 2 months reduced the levels of strong estrogen, and increased the levels of weak estrogen. But more importantly, the level of an estrogen metabolite associated with breast and endometrial cancer, 16--a-hydroxyestrone, was reduced by I3C (Bradlow et al. 1991).

When I3C changes "strong" estrogen to "weak" estrogen, the growth of human cancer cells is inhibited by 54-61% (Telang et al. 1997). Moreover, I3C provoked cancer cells to self-destruct (kill themselves via apoptosis). Induction of cell death is an approach to suppress carcinogenesis and is the prime goal of cytotoxic chemotherapy. The increase in apoptosis induced by I3C before initiation of new tumor development may contribute to suppression of tumor progression. Nontoxic I3C can reliably facilitate apoptosis (12 week treatment in rats); thus, this phytonutrient may become a standard adjunct in the treatment of breast cancer (Zhang et al. 2003)

I3C inhibits human breast cancer cells (MCF7) from growing by as much as 90% in culture; growth arrest does not depend on estrogen receptors (Cover et al. 1998). Furthermore, I3C induces apoptosis in tumorigenic (cancerous) but not in nontumorigenic (non-cancerous) breast epithelial cells (Rahman et al. 2003).

I3C does more than just turn strong estrogen to weak estrogen. 16-a-Hydroxyestrone (16-OHE) and 2-hydroxyestrone (2-OHE) are metabolites of estrogen in addition to estriol and estradiol. 2-OHE is biologically inactive, while 16-OHE is biologically active; that is, like estradiol, it can send "growth" signals. In breast cancer, the dangerous 16-OHE is often elevated, while the protective 2-OHE is decreased. Cancer-causing chemicals change the metabolism of estrogen so that 16-OHE is elevated. Studies show that people who take I3C have beneficial increases in the "weak" estriol form of estrogen and also increases in protective 2-OHE.

African-American women who consumed I3C, 400 mg for 5 days, experienced an increase in the "good" 2-OHE and a decrease of the "bad" 16-OHE. However, it was found that the minority of women who did not demonstrate an increase in 2-OHE, had a mutation in a gene that helps metabolize estrogen to the 2-OHE version. Those women had an eight times higher risk of breast cancer (Telang et al. 1997).

I3C Stops Cancer Cells from Growing

Tamoxifen is a drug prescribed to reduce breast cancer metastases and improve survival. I3C has modes of action similar to tamoxifen. I3C inhibited the growth of estrogen-receptor-positive breast cancer cells by 90% compared to 60% for tamoxifen. The mode of action attributed to I3C's impressive effect was interfering with the cancer cell growth cycle. Adding tamoxifen to I3C gave a 5% boost (95% total inhibition) (Cover et al. 1999).

In estrogen-receptor-negative cells, I3C stopped the synthesis of DNA by about 50%, whereas tamoxifen had no significant effect. I3C also restored p21 and other proteins that act as checkpoints during the synthesis of a new cell. Tamoxifen showed no effect on p21. Restoration of these growth regulators is extremely important. For example, tumor suppressor p53 works through p21 that I3C restores. I3C also inhibits cancers caused by chemicals. If animals are fed I3C before exposure to cancer-causing chemicals, DNA damage and cancer are virtually eliminated (Cover et al. 1999).

A study on rodents shows that damaged DNA in breast cells is reduced 91% by I3C. Similar results are seen in the liver (Devanaboyina et al. 1997). Female smokers taking 400 mg of I3C significantly reduced their levels of a major lung carcinogen. Cigarette chemicals are known to adversely affect estrogen metabolism (Taioli et al. 1997).

There is no proven way to prevent breast cancer, but the best and most comprehensive scientific evidence so far supports phytochemicals such as I3C (Meng et al. 2000). The results from a placebo-controlled, double-blind dose-ranging chemoprevention study on 60 women at increased risk for breast cancer demonstrated that I3C at a minimum effective dosage 300 mg per day is a promising chemopreventive agent for breast cancer prevention (Wong et al. 1997). The results of a single-blind phase I trial which studied the effectiveness of I3C in preventing breast cancer in nonsmoking women who are at high risk of breast cancer are awaited. The rationale for this study is that I3C, ingested twice daily, may be effective at preventing breast cancer.

I3C was found to be superior to 80 other compounds, including tamoxifen, for anticancer potential. Indoles, which down-regulate estrogen receptors, have been proposed as promising agents in the treatment and prevention of cancer and autoimmune diseases such as multiple sclerosis, arthritis, and lupus. Replacement of all the chemically altered estrogen drugs, such as tamoxifen, with a new generation of chemically altered indole drugs that fit in the aryl-hydrocarbon (Ah) receptor and regulate estrogen indirectly may prove beneficial to cancer patients (Bitonti et al. 1999). An I3C tetrameric derivative (chemically derived) is currently a novel lead inhibitor of breast cancer cell growth, considered a new, promising therapeutic agent for both ER+ and ER- breast cancer (Brandi et al. 2003).

A summary of studies shows that indole-3-carbinol (I3C) can:

- Increase the conversion of estradiol to the safer estriol by 50% in healthy people in just 1 week (Michnovicz et al. 1991)
- Prevent the formation of the estrogen metabolite, 16,alpha-hydroxyestrone, that prompts breast cancer cells to grow (Chen et al. 1996), in both men and women in 2 months (Michnovicz et al. 1997)
- Stop human cancer cells from growing (54-61%) and provoke the cells to self-destruct (apoptosis) (Telang et al. 1997)
- Inhibit human breast cancer cells (MCF7) from growing by as much as 90% in vitro (Ricci et al. 1999)
- Inhibit the growth of estrogen-receptor-positive breast cancer cells by 90%, compared to tamoxifen's 60%, by stopping the cell cycle (Cover et al. 1999)
- Prevent chemically induced breast cancer in rodents by 70-96%. Prevent other types of cancer, including aflatoxin-induced liver cancer, leukemia, and colon cancer (Grubbs et al. 1995)
- Inhibit free radicals, particularly those that cause the oxidation of fat (Shertzer et al. 1988)
- Stop the synthesis of DNA by about 50% in estrogen-receptor-negative cells, whereas tamoxifen had no significant effect (Cover et al. 1998)
- Restore p21 and other proteins that act as checkpoints during the synthesis of a new cancer cell. Tamoxifen has no effect on p21 (Cover et al. 1998)
- Virtually eliminate DNA damage and cancer prior to exposure to cancer-causing chemicals (in animals fed I3C) (Grubbs et al. 1995)
- Reduce DNA damage in breast cells by 91% (Devanaboyina et al. 1997)
- Reduce levels of a major nitrosamine carcinogen in female smokers (Taioli et al. 1997)

How to Use I3C
While the evidence is compelling, it is too soon to know exactly how effective I3C will be as an adjuvant breast cancer therapy (see the Breast Cancer References for citations pertaining specifically to I3C).

Suggested dosage: Take one 200-mg capsule of I3C twice a day, for those under 120 pounds. For those who weigh more than 120 pounds, three 200-mg capsules a day are suggested. Women who weigh over 180 pounds should take four 200-mg I3C capsules a day.

Note: A little is good; a lot is not necessarily better. Too much I3C can have the opposite effect; therefore, do not exceed the suggested dosage.

Caution: Pregnant women should not take I3C because of its modulation of estrogen. I3C appears to act both at the ovarian and hypothalamic levels, whereas tamoxifen appears to act only on the hypothalamic-pituitary axis as an anti-estrogen. Both I3C and tamoxifen block ovulation by altering preovulatory concentrations of luteinizing hormone (LH) and follicle stimulating hormone (FSH) (Gao et al. 2002). The reported aversion to cruciferous vegetables by pregnant women may be associated with their ability to change estrogen metabolism. Estrogen is a necessary growth factor for the fetus.

Curcumin
Curcumin is extracted from the spice turmeric and is responsible for the orange/yellow pigment that gives the spice its unique color. Turmeric is a perennial herb of the ginger family and a major component of curry powder. Chinese and Indian people, both in herbal medicine and in food preparation, have safely used it for centuries.

Curcumin has a number of biological effects in the body. However, one of the most important functions is curcumin's ability to inhibit growth signals emitted by tumor cells that elicit angiogenesis (growth and development of new blood vessels into the tumor).

Curcumin inhibits the epidermal growth factor receptor and is up to 90% effective in a dose-dependent manner. It is important to note that while curcumin has been shown to be up to 90% effective in inhibiting the expression of the epidermal growth factor receptor on cancer cell membranes, this does not mean it will be effective in 90% of cancer patients or reduce tumor volume by 90%. However, because two-thirds of all cancers overexpress the epidermal growth factor receptor and such overexpression frequently fuels the metastatic spread of the cancer throughout the body, suppression of this receptor is desirable.

Other anticancer mechanisms of curcumin include:

- Inhibition of the induction of basic fibroblast growth factor (bFGF). bFGF is both a potent growth signal (mitogen) for many cancers and an important signaling factor in angiogenesis (Arbiser et al. 1998).
- Antioxidant activity. In vitro it has been shown to be stronger than vitamin E in prevention of lipid peroxidation (Sharma 1976; Toda et al. 1985).

- Inhibition of the expression of COX-2 (cyclooxygenase 2), the enzyme involved in the production of prostaglandin E2 (PGE-2), a tumor-promoting hormone-like agent (Zhang et al. 1999).
- Inhibition of a transcription factor in cancer cells known as nuclear factor-kappa B (NF-KB). Many cancers overexpress NF-KB and use this as a growth vehicle to escape regulatory control (Bierhaus et al. 1997; Plummer et al. 1999).
- Increased expression of nuclear p53 protein in human basal cell carcinomas, hepatomas, and leukemia cell lines. This increases apoptosis (cell death) (Jee et al. 1998).
- Increases production of transforming growth factor-beta (TGF-beta), a potent growth inhibitor, producing apoptosis (Park et al. 2003; Sporn et al. 1989).
- TGF-beta is known to enhance wound healing and may play an important role in the enhancement of wound healing by curcumin (Mani H et al. 2002; Sidhu et al. 1998).
- Inhibits PTK (protein tyrosine kinases) and PKC (protein kinase C). PTK and PKC both help relay chemical signals through the cell. Abnormally high levels of these substances are often required for cancer cell signal transduction messages. These include proliferation, cell migration, metastasis, angiogenesis, avoidance of apoptosis, and differentiation (Reddy et al. 1994; Davidson et al. 1996).
- Inhibits AP-1 (activator protein-1) through a non-antioxidant pathway. While curcumin is an antioxidant (Kuo et al. 1996), it appears to inhibit signal-transduction via protein phosphorylation thereby decreasing cancer-cell activity, regulation, and proliferation (Huang et al. 1991).

Based on the favorable, multiple mechanisms listed above, higher-dose curcumin would appear to be useful for cancer patients to take. However, as far as curcumin being taken at the same time as chemotherapy drugs, there are contradictions in the scientific literature. Therefore, caution is advised. Please refer to the Cancer Chemotherapy protocol before considering combining curcumin with chemotherapy.

Curcumin's effects are a dose dependent response, and a standardized product is essential. The recommended dose is four 900-mg capsules 3 times per day, preferably with food.

Breast Cancer

Green Tea

As a tumor grows it elicits new capillary growth (angiogenesis) from the surrounding normal tissues and diverts blood supply and nutrients away from the tissue to feed itself. Unregulated tumor angiogenesis can facilitate the growth of cancer throughout the body. Antiangiogenesis agents, including green tea, inhibit this new tumor blood vessel (capillary) growth.

Green tea contains epigallocatechin gallate EGCG, a polyphenol that helps to block the induction of vascular endothelial growth factor (VEGF). Scientists consider VEGF essential in the process of angiogenesis and tumor endothelial cell survival. It is the EGCG fraction of green tea that makes it a potentially effective adjunct therapy in the treatment of breast cancer. In vivo studies have shown green tea extracts to have the following actions on human cancer cells (Jung et al. 2001b; Muraoka et al. 2002):

- Inhibition of tumor growth by 58%
- Inhibition of activation of nuclear factor-kappa beta
- Inhibition of microvessel density by 30%
- Inhibition of tumor-cell proliferation in vitro by 27%
- Increased tumor-cell apoptosis 1.9-fold
- Increased tumor endothelial-cell apoptosis threefold

The most current research shows that green tea may have a beneficial effect in treating cancer. While drinking green tea is a well-documented method of preventing cancer, it is difficult for the cancer patient to obtain a sufficient quantity of EGCG anticancer components in that form. Standardized green tea extract is more useful then green tea itself because the dose of EGCG can be precisely monitored and greater doses can be ingested without excessive intake of liquids. A suggested dose for a person with breast cancer is 5 capsules of 350-mg lightly caffeinated green tea extract 3 times a day with each meal. Each capsule should provide at least 100 mg of EGCG. It may be desirable to take a decaffeinated version of green tea extract in the evening to ensure that the caffeine does not interfere with sleep. Those sensitive to caffeine may also use this decaffeinated form.

However, there are benefits to obtaining some caffeine. Studies show that caffeine potentiates the anticancer effects of tea polyphenols, including the critical EGCG. Caffeine will be discussed in further detail later in this protocol. Green tea extract is available in a decaffeinated form for those sensitive to caffeine or those who want to take the less-stimulating decaffeinated green tea extract capsules for their evening dose.

Conjugated Linoleic Acid (CLA)

Conjugated linoleic acid (CLA) found naturally, as a component of beef and milk, refers to isomers of octadecadienoic acid with conjugated double bonds. CLA is essential for the transport of dietary fat into cells, where it is used to build muscle and produce energy. CLA is incorporated into the neutral lipids of mammary fat (adipocyte) cells, where it serves as a local reservoir of CLA. It has been proposed that CLA may be an excellent candidate for prevention of breast cancer (Ip et al. 2003). Low levels of CLA are found in breast cancer patients but these do not influence survival. Nevertheless, it has been hypothesized that a higher intake of CLA might have a protective effect on the risk of metastasis (Chajes et al. 2003).

CLA was shown to prevent mammary cancer in rats if given before the onset of puberty. CLA ingested during the time of the "promotion" phase of cancer development conferred substantial protection from further development of breast cancer in the rats by inducing cell kill of pre-cancerous lesions (Ip et al. 1999b). It was determined that feeding CLA to female rats while they were young and still developing conferred life-long protection against breast cancer. This preventative action was achieved by adding enough CLA to equal 0.8% of the animal's total diet (Ip et al. 1999a).

CLA inhibits the proliferation of human breast cancer cells (MCF-7), induced by estradiol and insulin (but not EGF). In fact, CLA caused cell kill (cytotoxicity) when tumor cells were induced with insulin (Chujo et al. 2003). The antiproliferative effects of CLA are partly due to their ability to elicit a p53 response that leads to growth arrest (Kemp et al. 2003). CLA elicits cell killing effects in human breast tumor cells through both p53-dependent and p53 independent pathways according to the cell type (Majumder et al. 2002). Refer to Cancer Treatment The Critical Factors, for more information on determining the p53 status of cancer. The effects of CLA are mediated by both direct action (on the epithelium) as well as indirect action through the stroma.

The growth suppressing effect of CLA may be partly due to changes in arachidonic distribution among cellular lipids and an altered prostaglandin profile (Miller et al. 2001). Intracellular lipids may become more susceptible to oxidative stress to the point of producing a cytotoxic effect (Devery et al. 2001). CLA has the ability to suppress arachidonic acid. Since arachidonic acid can produce inflammatory compounds that can promote cancer proliferation, this may be yet another explanation for CLA's anticancer effects.

Life Extension's recommendation for CLA is a dose of 3000-4000 mg daily, which is approximately 1% of the average human diet. The suggested amount required to obtain the overall cancer-preventing effects is only 3000-4000 mg daily in divided doses.

CLA may work via a mechanism similar to that of antidiabetic drugs not only by enhancing insulin-sensitivity but also by increasing plasma adiponectin levels, alleviating hyperinsulinemia (Nagao et al. 2003) protecting against cancer. A number of human cancer cell lines express the PPAR-gamma transcription factor, and agonists for PPAR-gamma can promote apoptosis in these cell lines and impede their clonal expansion both in vitro and in vivo. CLA can activate PPAR-gamma in rat adipocytes, possibly explaining CLA's antidiabetic effects in Zucker fatty rats. A portion of CLA's broad-spectrum anticarcinogenic activity is probably mediated by PPARgamma activation in susceptible tumor (McCarty 2000). However, CLA's anticarcinogenic effects could not be confirmed in one epidemiologic study in humans (Voorips et al. 2002). (Note: The term PPAR-gamma is an acronym for peroxisome proliferator-activatedreceptor-gamma. A PPAR-gamma agonist such as Avandia, Actos, or CLA activates the PPAR-gamma receptor. This class of drug is being investigated as a potential adjuvant therapy against certain types of cancer.)

Note: A combination product called Super CLA with Guarana may be used instead of CLA alone. Guarana is an herb that contains a form of caffeine called guaranine, which is 2.5 times stronger than the caffeine found in coffee, tea, and caffeinated soft drinks. What makes guaranine a unique source of caffeine is its slower release due to the guarana seed, which is fatty (even in powder form) as opposed to water-soluble. Caffeine has an inhibitory effect on the growth of cancer and is synergistic with other natural anticancer compounds.

Caffeine

Caffeine occurs naturally in green tea and has been shown to potentiate the anticancer effects of tea polyphenols. Caffeine is a model radio-sensitizing agent that is thought to work by abolishing the radiation-induced G2-phase checkpoint in the cell cycle. Caffeine can induce apoptosis of a human lung carcinoma cell line by itself and it can act synergistically with radiation to induce tumor cell kill and cell growth arrest. The cancer cell killing effect of caffeine is dependent on the dose (Qi et al. 2002).

Caffeine enhances the tumor cell killing effects of anticancer drugs and radiation. A preliminary report on radiochemotherapy combined with caffeine for high-grade soft tissue sarcomas in 17 patients, (treated with cisplatin, caffeine, and doxorubicin after radiation therapy) determined complete response in six patients, partial response in six and no change in five patients. The effectiveness rate of caffeine-potentiated radiochemotherapy was therefore 17%, and contributed to a satisfactory local response and the success of function-saving surgery for high-grade soft tissue sarcomas (Tsuchiya et al. 2000).

In a randomized, double blind placebo-controlled crossover study, the effects of caffeine as an adjuvant to morphine in advanced cancer patients was found to benefit the cognitive performance and reduce pain intensity (Mercadente et al. 2001).

Cancer patients should note that one study demonstrated that caffeine reduced the cytotoxic effect of paclitaxel on human lung adenocarcinoma cell lines (Kitamoto et al. 2003).

To ascertain the inhibitory effects of caffeine, mice at high risk of developing malignant and nonmalignant tumors (SKH-1), received oral caffeine as their sole source of drinking fluid for 18-23 weeks. Results revealed that caffeine inhibited the formation and decreased the size of both nonmalignant tumors and malignant tumors (Lou et al. 1999).

In cancer cells, p53 gene mutations are the most common alterations observed (50-60%) and are a factor in both carcinomas and sarcomas. Caffeine has been shown to potentiate the destruction of p53-defective cells by inhibiting p53's growth signal. The effects of this are to inhibit and override the DNA damage-checkpoint and thus kill dividing cells. Caffeine uncouples cell-cycle progression by interfering with the replication and repair of DNA(Sakurai et al. 1999; Ribeiro et al. 1999; Jiang et al. 2000; Valenzuela et al. 2000).

Caffeine inhibits the development of Ehrlich ascites carcinoma in female mice (Mukhopadhyay 2001). Topical application of caffeine inhibits the occurrence of cancer and increases tumor cell death in radiation-induced skin tumors in mice (Lu et al. 2002). Caffeine inhibits solid tumor development and lung experimental metastasis induced by melanoma cells (Gude et al. 2001).

Consumption of coffee, tea, and caffeine was not associated with breast cancer incidence in a study of 59,036 Swedish women (aged 40-76 years) (Michels et al. 2002).

Melatonin

One of the most important supplements for a breast cancer patient is the hormone melatonin. Melatonin inhibits human breast cancer cell growth (Cos et al. 2000) and reduces tumor spread and invasiveness in vitro (Cos et al.1998). Indeed, it has been suggested that melatonin acts as a naturally occurring anti-estrogen on tumor cells, as it down-regulates hormones responsible for the growth of hormone-dependent mammary tumors (Torres-Farfan 2003).

A high percentage of women with estrogen-receptor-positive breast cancer have low plasma melatonin levels (Brzezinski et al. 1997). There have been some studies demonstrating changes in melatonin levels in breast cancer patients; specifically, women with breast cancer were found to have lower melatonin levels than women without breast cancer (Oosthuizen et al. 1989). Normally, women undergo a seasonal variation in the production of certain hormones, such as melatonin. However, it was found that women with breast cancer did not have a seasonal variation in melatonin levels, as did the healthy women (Holdaway et al. 1997).

Low levels of melatonin have been associated with breast cancer occurrence and development. Women who work predominantly at night and are exposed to light, which inhibits melatonin production and alters the circadian rhythm, have an increased risk of breast cancer development (Schernhammer et al. 2003). In contrast, higher melatonin levels have been found in blind and visually impaired people, along with correspondingly lower incidences of cancer compared to those with normal vision, thus suggesting a role for melatonin in the reduction of cancer incidence (Feychting et al. 1998).

Light at night, regardless of duration or intensity, inhibits melatonin secretion and phase-shifts the circadian clock, possibly altering the cell growth rate that is regulated by the circadian rhythm (Travlos et al. 2001). Disruption of circadian rhythm is commonly observed among breast cancer patients (Mormont et al. 1997; Roenneberg et al. 2002) and contributes to cancer development and tumor progression. The circadian rhythm alone is a statistically significant predictor of survival time for breast cancer patients (Sephton et al. 2000).

Melatonin differs from the classic anti-estrogens such as tamoxifen in that it does not seem to bind to the estrogen receptor or interfere with the binding of estradiol to its receptor (Sanchez-Barcelo 2003). Melatonin does not cause side effects, such as those) caused by the conventional anti-estrogen drug tamoxifen. Furthermore, when melatonin and tamoxifen are combined, synergistic benefits occur. Moreover, melatonin can increase the therapeutic efficacy of tamoxifen (Lissoni et al.1995) and biological therapies such as IL-2 (Lissoni et al. 1994).

How melatonin interferes with estrogen signaling is unknown, though recent studies suggest that it acts through a cyclic adenosine monophosphate (cAMP)-independent signaling pathway (Torres-Farfan 2003). It has been proposed that melatonin suppresses the epidermal growth factor receptor (EGF-R) (Blask et al. 2002) and exerts its growth inhibitory effects by inducing differentiation ("normalizing" cancer cells)(Cos et al. 1996). Melatonin directly inhibits breast cancer cell proliferation (Ram et al. 2000) and boosts the production of immune components, including natural killer cells (NK cells) that have an ability to kill metastasized cancer cells.

In tumorigenesis studies, melatonin reduced the incidence and growth rate of breast tumors and slowed breast cancer development (Subramanian et al. 1991). Furthermore, prolonged oral melatonin administration significantly reduced the development of existing mammary tumors in animals (Rao et al. 2000).

In vitro experiments carried out with the ER-positive human breast cancer cells (MCF-7 cells), demonstrated that melatonin, at a physiological concentration (1 nM) and in the presence of serum or estradiol (a) inhibits, in a reversible way, cell proliferation, (b) increases the expression of p53 and p21WAF1 proteins and modulates the length of the cell cycle, and (c) reduces the metastatic capacity of these cells and counteracts the stimulatory effect of estradiol on cell invasiveness. Further, this effect is mediated, at least in part, by a melatonin-induced increase in the expression of the cell surface adhesion proteins E-cadherin and beta (1)-integrin (Sanchez-Barcelo et al. 2003).

Melatonin can be safely taken for an indefinite period of time. The suggested dose of melatonin for breast cancer patients is 3-50 mg at bedtime. Initially, if melatonin is taken in large doses vivid dreams and morning drowsiness may occur. To avoid these minor side effects melatonin may be taken in low doses nightly and the dose slowly increased over a period of several weeks.

Se-Methylselenocysteine

Se-methylselenocysteine (SeMSC), a naturally occurring organic selenium compound found to be an effective chemopreventive agent is a new and better form of selenium. SeMSC is a selenoamino acid that is synthesized by plants such as garlic and broccoli. Methylselenocysteine (MSC) has been shown to be effective against mammary cell growth both in vivo and in vitro (Sinha et al. 1999) and has significant anticancer activity against mammary tumor development (Sinha et al. 1997). Moreover, Se-methylselenocysteine was one of the most effective selenium chemoprevention compounds and induced apoptosis in human leukemia cells (HL-60) in vitro (Jung et al. 2001a). Exposure to MSC blocks expansion of cancer colonies and premalignant lesions at an early stage by simultaneously modulating pathways responsible for inhibiting cell proliferation and enhancing apoptosis (Ip et al. 2000a).

Se-methylselenocysteine has been shown to:

- Produce a 33% better reduction of cancerous lesions than selenite.

- Produce a 50% decrease in tumor development.
- Induce cell death (apoptosis) in cancer cells.
- Inhibit cancer-cell growth (proliferation).
- Reduce density and development of tumor blood vessels.
- Down-regulate VEGF (vascular endothelial growth factor).

(Ip et al. 1992; Sinha et al. 1997; Sinha et al. 1999; Ip et al. 2000a, b; Dong et al. 2001)

Unlike MSC, which is incorporated into protein in place of methionine, SeMSC is not incorporated into any protein, thereby offering a completely bioavailable compound. In animal studies, SeMSC has been shown to be 10 times less toxic than any other known form of selenium. Breast cancer patients may consider taking 400 mcg of SeSMC daily.

Breast Cancer

CoQ10

Coenzyme Q10 (CoQ10) is synthesized in humans from tyrosine through a cascade of eight aromatic precursors. These precursors require eight vitamins, which are vitamin C, B2, B3 (niacin) B6, B12, folic acid, pantothenic acid, and tetrahydrobiopterin as their coenzymes.

Since the 1960s, studies have shown that cancer patients often have decreased blood levels of coenzyme Q10 (Lockwood et al. 1995; Folkers 1996; Ren et al. 1997). In particular, breast cancer patients (with infiltrative ductal carcinoma) who underwent radical mastectomy were found to have significantly decreased tumor concentrations of CoQ10 compared to levels in normal surrounding tissues. Increased levels of reactive oxygen species may be involved in the consumption of CoQ10 (Portakal et al. 2000). These findings sparked interest in the compound as a potential anticancer agent (NCCAM 2002). Cellular and animal studies have found evidence that CoQ10 stimulates the immune system and can increase resistance to illness (Bliznakov et al. 1970; Hogenauer et al. 1981; NCCAM 2002).

CoQ10 may induce protective effect on breast tissue and has demonstrated promise in treating breast cancer. Although there are only a few studies, the safe nature of CoQ10 coupled with this promising research of its bioenergetic activity suggests that breast cancer patients should take 100 mg up to 3 times a day. It is important to take CoQ10 with some kind of oil, such as fish or flax, because dry powder CoQ10 is not readily absorbed.

In a clinical study, 32 patients were treated with CoQ10 (90 mg) in addition to other antioxidants and fatty acids; six of these patients showed partial tumor regression. In one of these cases the dose of CoQ10 was increased to 390 mg and within one month the tumor was no longer palpable, within two months the mammography confirmed the absence of tumor. In another case, the patient took 300 mg of CoQ10 for residual tumor (post non-radical surgery) and within 3 months there was non residual tumor tissue (Lockwood et al. 1994). This overt complete regression of breast tumors in the latter two cases coupled with further reports of disappearance of breast cancer metastases (liver and elsewhere) in several other case (Lockwood et al. 1995) demonstrates the potential of CoQ10 in the adjuvant therapy of breast cancer.

There are promising results for the use of CoQ10 in protecting against heart damage related to chemotherapy. Many chemotherapy drugs can cause damage to the heart (UTH 1998; ACS 2000; NCCAM 2000; Dog et al. 2001), and initial animal studies found that CoQ10 could reduce the adverse cardiac effects of these drugs (Combs et al. 1977; Choe et al. 1979; Lubawy et al. 1980; Usui et al. 1982; Shinozawa et al. 1993; Folkers 1996).

Caution: Some studies indicate that CoQ10 should not be taken at the same time as chemotherapy. If this were true, it would be disappointing, because CoQ10 is so effective in protecting against adriamycin-induced cardiomyopathy. Adriamycin is a chemotherapy drug sometimes used as part of a chemotherapy cocktail. Until more research is known, it is not possible to make a definitive recommendation concerning taking CoQ10 during chemotherapy. For more information please see the Cancer Chemotherapy protocol.

EPA and DHA

Dietary polyunsaturated fatty acids (PUFAs) of the omega-6 (n-6) class, found in corn oil and safflower oil, may be involved in the development of breast cancer, whereas long chain (LC) omega-3 (n-3) PUFAs, found in fish oil can inhibit breast cancer (Bagga et al. 2002).

A case control study examining levels of fatty acids in breast adipose tissue of breast cancer patients has shown that total omega-6 PUFAs may be contributing to the high risk of breast cancer in the United States and that omega-3 PUFAs, derived from fish oil, may have a protective effect (Bagga et al. 2002).

A higher omega-3:omega-6 ratio ((n-3)):(n-6) ratio) may reduce the risk of breast cancer, especially in premenopausal women (Goodstine et al. 2003). In a prospective study of 35,298 Singapore Chinese women aged 45-74 years, it was determined that high levels of dietary omega-3 fatty acids from marine sources (fish/shellfish) were significantly associated with reduced risk of breast cancer. Furthermore, women who consumed low levels of marine omega-3 fatty acids had a statistically significant increased risk of breast cancer (Gago-Dominguez et al. 2003).

Omega-3 fatty acids, primarily eicosapentanoic acid (EPA) and docosahexaneoic acid (DHA) found naturally in oily fish and fish oil, have been consistently shown to retard the growth of breast cancer in vitro and in animal experiments, inhibit tumor development and metastasis. Fish oils have antiproliferative effects at high doses, which means they can inhibit tumor cell growth, through a free radical-mediated mechanism, while at more moderate doses omega-3 fatty acids inhibit, Ras protein activity, angiogenesis, and inflammation. The production of pro-inflammatory cytokines can be modified by dietary omega-3 PUFAs

(Mancuso et al. 1997).

High consumption of fatty fish is weakly associated with reduced breast cancer risk (Goodstine et al. 2003). Flaxseed, the richest source of alpha-linoleic acid inhibited the established growth and metastasis of human breast cancer implanted in mice. This effect was found to be due to its down-regulation of insulin-like growth factor I (IGF-1) and epidermal growth factor receptor (EGF-R) expression (Chen et al. 2002). The recommended dosage is to consume a fish-oil concentrate supplement that provides 3200 mg of EPA and 2400 mg of DHA a day taken in divided doses.

Vitamins A, D, and E

Vitamin A and vitamin D3 inhibit breast cancer cell division and can induce cancer cells to differentiate into mature, noncancerous cells. Vitamin D3 works synergistically with tamoxifen (and melatonin) to inhibit breast cancer cell proliferation. The vitamin D-3 receptor as a target for breast cancer prevention was examined. Pre-clinical studies demonstrated that vitamin D compounds could reduce breast cancer development in animals. Furthermore, human studies indicate that both vitamin D status and genetic variations in the vitamin D-3 receptor (VDR) may affect breast cancer risk. Findings from cellular, molecular and population studies suggest that the VDR is a nutritionally modulated growth-regulatory gene that may represent a molecular target for chemoprevention of breast cancer (Welsh et al. 2003).

Daily doses of vitamin A, 350,000 to 500,000 IU were given to 100 patients with metastatic breast carcinoma treated by chemotherapy. A significant increase in the complete response was observed; however, response rates, duration of response and projected survival were only significantly increased in postmenopausal women with breast cancer (Israel et al. 1985).

Breast cancer patients may take between 4000 to 6000 IU, of vitamin D3 every day. Water-soluble vitamin A can be taken in doses of 100,000-300,000 IU every day. Monthly blood tests are needed to make sure toxicity does not occur in response to these high daily doses of vitamin A and vitamin D3. After 4-6 months, the doses of vitamin D3 and vitamin A can be reduced.

Vitamin E is the term used to describe eight naturally occurring essential fat-soluble nutrients: alpha-, beta-, delta-, and gamma-tocopherols plus a class of compounds related to vitamin E called alpha-, beta-, delta-, and gamma-tocotrienols. Vitamin E from dietary sources may provide women with modest protection from breast cancer.

Vitamin E succinate, a derivative of fat-soluble vitamin E, has been shown to inhibit tumor cell growth in vitro and in vivo (Turley et al. 1997; Cameron et al. 2003). In estrogen receptor-negative human breast cancer cell lines vitamin E succinate, inhibited growth and induced cell death. Since vitamin E is considered the main chain breaking lipophilic antioxidant in plasma and tissue, its role as a potential chemopreventative agent and its use in the adjuvant treatment of aggressive human breast cancers appears reasonable. Those with estrogen-receptor-negative breast cancers should consider taking 800-1200 IU of vitamin E succinate a day. Vitamin E supplementation, 800 IU daily for 4 weeks, was shown to significantly reduce hot flashes in breast cancer survivors (Barton et al. 1998).

Caution: Refer to the symptoms of vitamin A toxicity in Appendix A: Avoiding Vitamin A Toxicity. When taking doses of vitamin D3 in excess of 1400 IU a day, regular blood chemistry tests should be taken to monitor kidney function and serum calcium metabolism. Vitamin E has potential blood thinning properties, individuals taking anticoagulant drugs should inform their treating physician if supplementing with vitamin E and have their clotting factors monitored regularly.

Tocotrienols

When vitamin E was isolated from plant oils, the term tocopherols was used to name the initial four compounds that shared similar structures. Their structures have two primary parts--a complex ring and a phytyl (long-saturated) side chain--and have been designated as alpha, beta, delta, and gamma tocopherol. Tocopherols (vitamin E) are important lipid-soluble antioxidants that can protect the body against free radical damage.

However, there are four additional compounds related to tocopherols--called tocotrienols?that are less widely distributed in nature. The tocotrienol structure, three double bonds in an isoprenoid (unsaturated) side chain, differs from that of tocopherols. While tocopherols are found in corn, olive oil, and soybeans, tocotrienols are concentrated in palm, rice bran, and barley oils.

Tocotrienols elicit powerful anticancer properties, and studies have confirmed tocotrienol activity is much stronger than that of tocopherols (Schwenke et al. 2002).

Tocotrienols provide more efficient penetration into tissues such as the brain and liver. Because of the double bonds in the isoprenoid side chain, tocotrienols move freely and more efficiently within cell membranes than tocopherols, giving tocotrienols greater ability to counteract free radicals. This greater mobility also allows tocotrienols to recycle more quickly than alpha-tocopherol. Tocotrienols are better distributed in fatty cell membranes and demonstrate greater antioxidant and free-radical-scavenging effects than that of vitamin E (alpha-tocopherol) (Serbinova et al. 1991; Theriault et al. 1999).

Tocotrienol's antioxidant function is associated with lowering DNA damage, tumor formation, and of cell damage. Animals exposed to carcinogens that were fed corn oil- or soybean oil-based diets had significantly more tumors than those fed a tocotrienol-rich palm oil diet. Tocotrienol-rich palm oil did not promote chemically induced breast cancer (Sundram et al. 1989).

Tocotrienols possess the ability to stimulate the selective killing of cancer cells through programmed cell death (apoptosis) and to reduce cancer cell proliferation while leaving normal cells unaffected (Kline et al. 2001). Tocotrienols are thought to suppress cancer through the isoprenoid side chain.

Isoprenoids are plant compounds that have been shown to suppress the initiation, growth, and progression of many types of cancer in experimental studies (Block et al. 1992). They are common in fruits and vegetables, which may explain why diets rich in these foods have consistently been shown to reduce the incidence of cancer.

Isoprenoids induce cell death (apoptosis) and arrest cell growth in human breast adenocarcinoma cells (MCF-7) (Mo et al.1999). Isoprenoids may suppress the mevalonate pathway, through which mutated Ras proteins transform healthy cells into cancer cells. Mutated ras is the most common cellular defect found in human cancers. The mevalonate pathway escapes regulatory control in tumor tissue but remains highly sensitive to regulation by tocotrienols. Tocotrienols are at least five times more powerful than farnesol, the body's regulator of the mevalonate pathway. Interestingly, human breast cancer cells have been shown to respond very well to treatment with tocotrienols (Parker et al. 1993).

Tocotrienols cause growth inhibition of breast cancer cells in culture independent of estrogen sensitivity and have great potential in the prevention and treatment of breast cancer (Nesaretnam et al. 1998).

In vitro studies have demonstrated the effectiveness of tocotrienols as inhibitors of both estrogen-receptor-positive (estrogen-responsive) and estrogen-receptor-negative (nonestrogen-responsive) cell proliferation. The effect of palm tocotrienols on three human breast cancer cells lines, estrogen-responsive and estrogen-nonresponsive (MCF7, MDA-MB-231, and ZR-75-1), found that tocotrienols inhibited cell growth strongly in both the presence and absence of estradiol. The gamma- and delta-fractions of tocotrienols were most effective at inhibiting cell growth, while alpha-tocopherol was ineffective. Tocotrienols were found to enhance the effect of tamoxifen (Nesaretnam et al. 2000).

Delta-tocotrienol was shown to be the most potent inducer of apoptosis (programmed cell death) in both estrogen-responsive and estrogen-nonresponsive human breast cancer cells, followed by gamma- and alpha-tocotrienol (beta-tocotrienol was not tested). Interestingly, delta-tocotrienol is more plentiful in palm tocotrienols than in tocotrienols derived from rice. Of the natural tocopherols, only delta-tocopherol showed any apoptosis-inducing effect, although it was less than one tenth of the effect of palm and rice delta-tocotrienol (Yu et al. 1999).

Tocotrienols effectively arrested the cell cycle and triggered cell death of mammary cancer cells (from mice) whereas tocopherols (alpha, gamma, and delta) did not cause inhibition of tumor cell growth. Highly malignant cells were most sensitive to the antiproliferative effects of tocotrienols, whereas less aggressive precancerous cells were the least sensitive (McIntyre et al. 2000).

Tocotrienols were found to be far more effective than alpha-tocopherol in inhibiting breast cancer cell growth. Tocotrienols in combination with tamoxifen proved more effective than either compound alone in both estrogen-responsive and nonresponsive breast cancer cells. The synergism between tamoxifen and tocotrienols may reduce the risk of adverse side effect from tamoxifen (Guthrie et al. 1997).

Tocotrienols are considered important lipid-soluble antioxidants, with potent anticancer and anti-inflammatory activity. Therefore, a daily dose of 240 mg of tocotrienols should be considered as an adjuvant breast cancer therapy.

PREVENTING BREAST CANCER CELL METASTASIS

- Bone Remodeling
- Bone Metastases Affects Remodeling
- Bone Loss and Fatty Acids
- Hormone Therapy and Metastasis

Breast cancer cells frequently metastasize to the bone, where they cause severe degradation of bone tissue. Metastatic cancer affects more than half of all women during the course of their disease. Bone metastases are a significant cause of morbidity due to pain, pathological fractures, hypercalcemia (abnormally high levels of calcium in blood plasma), and spinal cord compression. The bisphosphonates, including alendronate (Fosamax), tiludronate (Skelid), pamidronate (Aredia), etidronate (Didronel), risedronate (Actonel), ibandronate, and zoledronic acid (Zometa), are a class of drugs that protect against the degradation of bone, primarily by

inhibiting osteoclast-mediated bone resorption (bone breakdown).

Bisphosphonates are analogs of a naturally occurring compound, called pyrophosphate, which serves to regulate calcium and prevent bone breakdown. Bisphosphonates are a major class of drugs used for the treatment of bone diseases as they have a marked ability to inhibit bone resorption. Bisphosphonates are considered standard care for tumor-associated hypercalcemia and have been shown to reduce bone pain, improve quality of life, and to delay and reduce skeletal events (Hortobagyi 1996; Roemer-Becuwe et al. 2003).

Bone Remodeling

The renewal of bone is responsible for bone strength throughout our life. Old bone is removed (resorption) and new bone is created (formation). This process is called bone remodeling. Healthy bone is continually being remodeled. Two main types of cells are responsible for bone renewal: the osteoblasts involved in bone formation and the osteoclasts involved in bone resorption. There are several stages involved in bone remodeling. The first is activation. This process involves preosteoclasts that are stimulated and differentiated under the influence of cytokine and growth factors to mature into active osteoclasts. The next step is resorption, in which osteoclasts digest mineral matrix (old bone). The third step is reversal, which ends resorption and signals for the final phase, formation. During this stage, osteoblasts are responsible for bone matrix synthesis (collagen production). Two other noncollagenous proteins are also formed: osteocalcin and osteonectin, together they form new bone.

Breast Cancer

Bone Metastases Affects Remodeling

In patients with bone metastases, bone resorption by the osteoclasts is increased and exceeds bone reformation. Calcium lost from the bones appears in increased amounts in the patient's blood serum and urine. This increase in bone resorption may result in pain, bone fractures, spinal cord compression, and hypercalcemia.

Normally, the activity of the osteoclasts and osteoblasts is well-balanced, with the osteoclasts cleaning out the fatigued bone and the osteoblasts rebuilding new bone. In metastatic cancer, there is - increased osteoclast activity caused by factors called osteoclastic activating factors (OAFs). These OAFs released by tumor cells and include parathyroid hormone-related peptide (PTHrP), growth factors, and cytokines.

Among the known inhibitors of osteoclast activity, the bisphosphonates are the most promising drugs available (by prescription) to women with breast cancer who have a high risk of advancing cancer. Bisphosphonates interrupt the "vicious cycle" of bone metastases. Bisphosphonates inhibit bone turnover directly by decreasing resorption of bone and inhibiting the recruitment and function of osteoclasts.

Bisphosphonates may stop bone metastases from occurring if they are included at the onset of cancer diagnosis and treatment (ONI 2000). Bisphosphonates may delay the occurrence of bone metastases in women with breast cancer who do not have metastases.

In patients with bone metastases, bisphosphonates are useful as an adjuvant therapy to decrease bone pain, fractures, hypercalcemia, and progression of bone metastases (Delmas 1996). Treatment with bisphosphonates can also prevent the destruction of bone by cancer metastases and reduce the progression of metastatic tumors. A new bisphosphonate, risedronate, slows the progression of bone metastases in breast cancer patients, either by inhibiting the resorption of bone, which reduces the release of tumor growth factors, or by inhibiting the adhesion of breast cancer cells to bone matrix (Delmas 1996).

In women with early and advanced breast cancer and bone metastases the use of bisphosphonates (oral or intravenous) in addition to hormone therapy or chemotherapy reduced bone pain, the risk of developing a fracture, and increased the time to a fracture (Pavlakis et al. 2002). Monthly infusions of pamidronate in 382 women with Stage IV breast cancer and bone metastases significantly reduced the incidence and prolonged the median time of skeletal complications (Hortobagyi et al. 1996).

Bisphosphonates are now third generation and are often used in the treatment of lytic bone metastasis. They inhibit the osteoclast activity that causes elevation of the blood calcium level and osteolytic bone weakening. Osteolytic holes form as the cancer degrades the bone, making it prone to fracture (Cristfanilli et al. 1999)., The bisphosphonates, zoledronate and ibandronate, manage tumor-induced hypercalcemia, Paget's disease of the bone, and multiple myeloma-associated bone resorption. These bisphosphonate drugs are three orders of magnitude more potent than the first-generation drugs etidronate, clodronate, and tilundronate. Patients newly diagnosed with lytic bone metastasis of breast cancer are offered bisphosphonate therapy, such as intravenous zoledronate or pamidronate every 3 or 4 weeks, as long as it proves effective. Oral clodronate offers equivalent results but is less well-tolerated.

Women with primary breast cancer who receive chemotherapy, hormone therapy, aromatase therapy, or oophorectomy may experience ovarian failure or early menopause, leading to a loss of bone mineral density.

The mechanisms by which tumor cells degrade bone involve tumor-cell adhesion to bone, as well as the release of compounds from tumor cells that stimulate osteoclast-induced bone degradation. Bisphosphonates inhibit cancer-cell adhesion and inhibit osteoclast activity. By preventing tumor-cell adhesion, bisphosphonates are useful agents for the prophylactic treatment of patients with cancer that is known to preferentially metastasize to bone.

There is evidence that growth factors, such as insulin-like growth factor and transforming growth factor, are released when the bone matrix is degraded. These growth factors could stimulate tumor-cell proliferation throughout the body and may activate cancer cells to the degraded bone ripe for clonal development, which may be a reason that early use of bisphosphonates significantly improved survival and may ward off metastasis.

Based upon the mounting research, it is strongly recommended that the use of bisphosphonates be considered at onset of breast cancer treatment to potentially stop bone metastases from developing. Patients are urged to discuss the use of bisphosphonates with their physicians.

Note: Administration of bisphosphonate therapy should be accompanied by an adequate intake of a bone supplement that

supplies all the raw materials to make healthy bone. These include calcium, magnesium, boron, silica, vitamin D, and vitamin K. Do not take vitamin K with Coumadin or other anticoagulant drugs or blood thinners.

Bone Loss and Fatty Acids

While people often use omega-3 fatty acids to reduce the inflammation associated with arthritis, these fatty acids may actually help prevent bone loss. French researchers found in a group of 105 patients that high levels of pro-inflammatory omega-6 fatty acids were strongly associated with bone loss. However, the use of omega-3 supplements--360 mg a day of eicosapentanoic acid (EPA) and 240 mg a day of docosahexaneoic acid (DHA) - appeared to decrease production of pro-inflammatory prostaglandin E2 in bone and significantly stopped bone loss (Requirand et al. 2000).

Hormone Therapy and Metastasis

In primary breast cancer the estrogen receptor (ER) status represents an important prognostic factor and therefore, has a profound impact on the type of therapy employed. Yet, there is little research into the ER expression of disseminated breast cancer cells even though these cells are the main targets in adjuvant therapy.

A small pilot study involving 17 patients evaluated the ER expression profile on disseminated epithelial cells in bone marrow, one of the preferential organs for manifestation of distant metastases in breast cancer. Eleven patients (64.7%) were found to have ER-positive primary carcinomas. Of those eleven, only two patients revealed ER-positive epithelial cells in bone marrow. Additionally, one of these two patients expressed both ER-positive and ER-negative epithelial cells in bone marrow. Although in both of these cases the ER-positive epithelial cells in bone marrow derived from ER-positive primary tumors, in this small patient cohort none of the prognostic ally relevant clinical and pathological factors tested (i.e., TNM-classification, grading, and ER status in primary breast cancer) correlated with the ER status in bone marrow. A striking discrepancy between ER expression in primary breast cancers and the corresponding disseminated epithelial cells in bone marrow was found. This suggests either the selective dissemination of ER-negative tumor cells into the bone marrow or a negative impact of the bone marrow microenvironment on epithelial ER expression. While further research is required before conclusions can be drawn, this phenomenon might influence therapeutic effects of anti-hormonal treatment (Ditsch et al. 2003).

OTHER CONSIDERATIONS

Diet

Cancer has an appetite for sugar and requires sugar for survival. Sugar plays an active role in reducing the immune response and energizes cancer, as tumors are primarily obligate glucose metabolizers.

There is a relationship between lactic acid, insulin, and angiogenesis. In tumors, hypoxic conditions occur through both inflammation, which reduces blood flow, and the chaotic development of blood vessels within tumors. These hypoxic conditions alter the pathways by which immune cells and tumor cells burn fuel (glucose) for energy, creating excessive lactic acid. In an oxygen-rich (aerobic) environment, glucose is burned in an efficient process that produces a maximum amount of energy and a minimal amount of lactic acid. However, tumor cells in chronic hypoxic conditions produce excessive lactic acid and inefficient utilization of glucose. Thus, there is a vicious cycle in which the reduced energy output stimulates the tumor cells to burn more glucose, which in turn produces more lactic acid. Tumor cells consume glucose at a rate three to five times higher than normal cells, creating a highly stimulated glycolysis (glucose-burning) pathway.

This glucose consumption can waste the cancer patient's energy reserves, and the increased production of lactic acid can stimulate increased production of angiogenic factors. The macrophage-mediated angiogenesis creates a complex interplay between opposing regulators. Insulin plays an active roll in promoting angiogenesis. Insulin is a growth factor that stimulates glycolysis and the proliferation of many cancer-cell lines through tyrosine kinase growth factors (Boyd 2003). In cancer patients, elevated levels of insulin are common in cancerous tissue and blood plasma. Obesity, and early stages of Type-II noninsulin-dependent diabetes mellitus (NIDDM), has been implicated as risk factors in a variety of cancers.

Based upon cancer's sugar dependency, a sugar-deprivation diet is strongly recommended. An effective tool in eliminating sugar from the diet is through following the Glycemic Index. The index is a list that rates the speed at which foods are digested and raise blood sugar levels. The ratings are based upon the rate at which a measured amount of pure glucose affects the body's blood sugar curve. Glucose itself has a rating of 100, and the closer a food item is to a rating of 100, the more rapidly it raises blood glucose levels. Foods with a low Glycemic Index, such as vegetables, protein, and grains, are suggested (please refer to the Obesity protocol for specific information about low glycemic foods).

With regard to depleting sugar from the diet, the following should be considered:

- Limit or avoid all white foods, including (but not limited to) sugar, flour, rice, pasta, breads, crackers, cookies, etc.

- Read labels. Sugar has many names (brown sugar, corn syrup, honey, molasses, maple syrup, high-fructose corn syrup, dextrin, raw sugar, fructose, polyols, dextrose, hydrogenated starch, galactose, glucose, sorbitol, fruit juice concentrate, lactose, brown rice syrup, xylitol, sucrose, mannitol, sorghum, maltose, and turbinado, to mention only a few).
- Limit all fruit juices; per glass they contain the juice of many pieces of fruit and a large amount of fructose (fruit sugar) but no fiber. Instead, infrequently eat low glycemic-rated fruit in small portions.

Natural compounds have also been reported to inhibit the cancer-promoting effects of insulin. For example, vitamin C has been reported to increase oxygen consumption and reduce lactic acid production in tumor cells. In addition, some natural compounds may help reduce insulin production by reducing insulin resistance. Insulin resistance occurs when cells are no longer sensitive to insulin and thus more insulin is produced in an effort to reduce glucose levels. Insulin resistance has been implicated as a risk factor for breast cancer, and diets high in saturated fats and omega-6 fatty acids promote insulin resistance. Although the exact pathway is unknown, it is thought that the mechanism of action is via chronic activation of PKC. Some of the known natural compounds that can reduce insulin resistance include omega-3 fatty acids, curcumin, flavonoids, selenium, and vitamin E.

As discussed earlier in the protocol, estrogen is a growth factor for most breast cancers. High-fat diets and associated increases in fat tissue can increase estrogen availability in a number of ways:

- Fat tissue is a major source of estrogen production in postmenopausal women. Therefore, there is an association between high body weight and decreased survival in breast cancer patients.
- Obesity and possibly insulin resistance can decrease the levels of sex hormone binding globulin (SHBG) in both men and women and increase breast cancer risk or cancer progression. This is an important factor in estrogen-dependent breast cancer cells because it is adequate levels of SHBG that act as an anti-proliferative and provides an anti-estrogenic effect.
- Obesity can alter liver metabolism of estrogen, allowing the retention of high estrogen byproducts with high estrogenic activity within the body.
- High-fat diets may reduce the amount of estrogen excreted in the feces. In contrast, low-fat/high-fiber diets can reduce circulating estrogen.

Another consideration when discussing diet and breast cancer is the reduction of dietary estrogen. Several foods contain naturally occurring hormones (found in animal sources); synthetic hormones that can mimic estrogen in the human body (found in commercially packaged meat, poultry, and dairy products); or naturally estrogenic properties that can encourage the body's production of estrogens (natural foods such as soy). Regardless of the source, try to avoid all commercial animal products (including, but not limited to, meats, poultry, and dairy). Also avoid the use of soft plastic food-storage products that can give off large amounts of polymers (e.g., by leaching into food contents), thought by environmentalists and some researchers to be a possible cause of breast cancer.

In order to reduce estrogen, a breast cancer patient should consider increasing dietary intake of fish high in omega-3 fatty acids, whey, eggs, and nuts, occasionally including hormone-free poultry and hormone-free, low-fat dairy products.

BLOOD TESTING

Monthly blood tests should include complete blood chemistry, with tests for liver function and serum calcium levels, prolactin, parathyroid hormone, and the tumor marker CA 27.29 (or CA 15.3). Additional blood tests to consider are the CEA and GGTP tests. These tests monitor the progress of therapies used and also detect toxicity from high doses of vitamin A and vitamin D3. The patient should insist on obtaining a copy of their blood workups every month.

SUMMARY

When considering breast cancer treatment options, physicians and patients alike must sort through an overwhelming amount of information. This protocol attempts to simplify complicated scientific research and bring to the forefront the most up-to-date, multimodality approach to cancer treatment. It integrates surgery, anticancer drugs, irradiation, hormone therapy, nutritional supplementation, and diet modification in a comprehensive approach to counteract breast cancer.

As discussed in this protocol, cancer growth is based on many complicated interactions via numerous physiological pathways within the body. Despite the huge strides in scientific research, there are still many unanswered questions regarding cancer's growth and development. What we do know is that there is overwhelming research supporting an integrated approach to the treatment of cancer. Additionally, research supports using nutritional supplementation to improve the efficacy of chemotherapy drugs and radiotherapy (see the Cancer Chemotherapy and Cancer Radiation protocols for more information). In fact, combining certain supplements can create a synergism that can effectively block or impede certain cancer pathways.

Therefore, the supplementation regimen following is suggested. Please read the entire protocol before considering this regimen because there are certain cautions to consider. As always, consult your physician before beginning any nutritional supplementation regimen.

1. Indole-3-carbinol with Standarized Broccoli (I3C), one capsule per day for individuals weighing up to 179 pounds. Those weighing over 239 pounds, take two capsules per day. Indole-3-Carbinol with Standardized Broccoli also comes in a 300 mg dose for those weighing 180-239 pounds and only requires one capsule per day. **Caution:** Pregnant women should not take indole-3-carbinol because of its modulation of estrogen.
2. Curcumin, four 900 mg capsules, 3 times daily on an empty stomach for a total of 10.8 g per day. Note the caution earlier in this protocol.
3. Lightly caffeinated green tea extract, three 725 mg capsules, two times a day with meals. Use decaffeinated green tea extract if you are sensitive to caffeine or want to use the less-stimulating version with the evening dosage.
4. CLA or CLA with Guarana, 3000 to 4000 mg daily of CLA and about 300 mg of guarana, early in the day.
5. Melatonin, 3 to 50 mg at bedtime.
6. PhytoFood Powder (broccoli, cabbage, and other cruciferous vegetables that provide sulphoraphane and other cancer-fighting plant extracts), 1-2 tbsp daily.
7. Se-methylselenocysteine, 200 to 400 mcg daily.
8. CoQ10, three 100 mg softgels in divided doses. Note the caution stated in this protocol.
9. Super EPA/DHA w/Sesame Lignans, 8 softgels daily, in divided doses. Take with nonfiber meals.
10. Vitamin D3, 4000 to 6000 IU taken daily with monthly blood testing to monitor for toxicity. Reduce dosage at 6 months.
11. Water-soluble vitamin A, 100,000 to 300,000 IU daily with monthly blood testing to monitor for toxicity. Reduce dosage at 6 months (refer to vitamin A precautions in Appendix A).
12. Vitamin E succinate (tocopheryl succinate), 1200 IU daily.
13. Gamma E Tocopherol w/Sesame Lignans 1 capsule daily.
14. Vitamin C, 4000 to 12,000 mg throughout the day.
15. Gamma linolenic acid, 4 capsules of Mega GLA w/Sesame Lignans.
16. Whey protein concentrate-isolate, 30 to 60 grams daily in divided doses.
17. Bone Restore provides calcium, magnesium, and bone-protecting nutrients. Take 5 capsules at bedtime.
18. Vitamin K, 10 mg daily.
19. Silicon, 6 mg daily. (Jarrow's Biosil is recommended.)
20. Life Extension Mix without Copper (multinutrient formula), 3 tablets 3 times daily.

Reminder: Bisphosphonate (injectable Zometa or Aredia) drug therapy is strongly encouraged for all breast cancer patients as well as aromatase-inhibitor therapy (Arimidex, Femara, or Aromasin) if appropriate.

Note: If chemotherapy and/or radiation are being considered, refer to the Cancer Chemotherapy and Cancer Radiation protocols. Also refer to the protocols titled Cancer Treatment: The Critical Factors and Cancer Adjuvant Therapy.

FOR MORE INFORMATION

Contact the American Cancer Society, 1 (800) ACS-2345.

Sources for National Cancer Institute Information.

- Cancer Information Service, (800) 4-CANCER
  (1-800-422-6237); TTY (for hearing impaired callers), (800) 332-8615
- NCI Online /Internet, use http://cancer.gov to reach the NCI website.
- CancerMail Service, to obtain a contents list, send e-mail to cancermail@cips.nci.nih.gov with the word "help" in the body of the message.

PRODUCT AVAILABILITY

Indole-3-carbinol w/Standarized Broccoli (I3C), curcumin, green tea, CLA, CLA with guarana, melatonin, SeMsc (Se-methylselenocysteine), Super Absorbable CoQ10, Super EPA/ DHA w/Sesame Lignans, vitamin D3 caps, water-soluble vitamin A liquid, vitamin E succinate, Gamma E Tocopherol w/Sesame Lignans, vitamin C, Mega GLA/w Sesame Lignans, enhanced whey protein, Bone Restore, Phyto Food, vitamin K, Biosil, and Life Extension Mix can be ordered by calling (800) 544-4440 or by ordering online.

STAYING INFORMED

The information published in this protocol is only as current as the day the manuscript was sent to the printer. This protocol raises

many issues that are subject to change as new data emerge. Furthermore, cancer is still a disease with unacceptably high mortality rates, and none of our suggested regimens can guarantee a cure.

The Life Extension Foundation is constantly uncovering information to provide to cancer patients. A special website has been established for the purpose of updating patients on new findings that directly pertain to the published cancer protocols. Whenever Life Extension discovers information that may benefit cancer patients, it will be posted on the website www.lefcancer.org.

Before utilizing this cancer protocol, we suggest that check www.lefcancer.org to see if any substantive changes have been made to the recommendations described herein. Based on the sheer number of newly published findings, there could be significant alterations to the information you have just read.

◄ back

Mood Biochemistry of Women at Mid-life

Phyllis J. Bronson, Ph.D.[1]

Abstract

This study examines the effect of hormone and amino acid levels on mood changes in women at mid-life. The research involved both a clinical trial of the application of hormones and amino acids to effect mood changes is women at mid-life, and a laboratory analysis of synthetic and natural progesterones. The clinical trial involved a detailed biochemical study of two women and a less intensive study of two other groups of women identified as Estrogen Dominant or Estrogen Deficient. Depending on whether the women were Estrogen Dominant or Estrogen Deficient, they responded well to natural progesterone or estrogen, respectively. Even when natural estrogen was given, it was never without natural progesterone.

The clinical study found that a deficiency of progesterone is clearly implicated as a primary factor in mid-life anxiety patterns. Changes in serum levels correlated with the qualitative input given on questionnaires and interviews. Mid-life anxiety was more extreme during the latter two weeks of the menstrual cycle. The data showed that there is often too much estrogen to be mediated by the body's available progesterone. When neuro-inhibitory amino acids were used in conjunction with pharmaceutical grade, natural progesterone, women thrived and reported greatly increased calmness, even during the normally difficult pre-menstrual phase.

Laboratory analysis of synthetic and plant derived progesterone revealed significant differences in their structures and revealed discrepancies between the published and actual structure of the synthetic progesterone, Provera.® The primary distinction between natural progesterone and its synthetic counterpart turned out not to be in methylation, but rather in hydroxylation and the presence of acetate in the synthetic molecule. The laboratory analysis provides insight into why the two progesterones have different effects on women.

This pilot study has already had an important impact in the area of helping women solve the riddle of mid-life mood changes.

Clinical Research on Women at Mid-Life

This study focused on the moods and biochemistry of women at mid-life. Specifically it addressed the following issues:

1. Does a deficiency of progesterone affect anxiety patterns in mid-life or peri-menopausal females?
2. Is mid-life anxiety in women connected to low progesterone levels or estrogen dominance?
3. Are amino acids and/or plant-based hormones effective in the treatment of anxiety?

Definition of Terms

Estrogen Dominance: Estrogen levels, measured as dominant estradiol E2, that are too high relative to progesterone levels.

Estrogen Deficiency: A low level of estrogen, measured as serum estradiol, at either follicular, mid- cycle or luteal periods.

Laboratory Analysis of Natural and Synthetic Progesterone

This section of the research delved deeper into the molecular structures of natural, plant-derived progesterone and synthetic progesterone. The question here was: Are there structural differences between plant-derived and synthetic progesterones that can account for differences in their effects on women?

Methods

Clinical Trials

The subjects of this study fall into three groups.

1. Two women (the author being one of

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them) who were intensively studied and for whom relatively large numbers of blood samples were taken.

2. Six women showing tendencies toward "Estrogen Dominance"

3. Six women showing tendencies toward "Estrogen Deficiency"

The second and third groups were comprised of women followed over time, but for whom the blood samples were not taken as frequently as in the intensive group. All women reported here were informed of the nature of study and agreed to participate. Each of them was guaranteed the confidentiality of the data and signed a consent form for participation.

Formulation of Natural and Synthetic Hormones

Pharmaceutical grade, trans-dermal hormone creams were formulated by the Women's International Pharmacy. Both the estrogen and progesterone were extracted from a soy base. Users of this cream were subjected to regularly scheduled blood tests to determine how the use of this product affected their progesterone levels. Their reports of feeling depressed or anxious were correlated with what their blood tests actually showed.

Questions on Mood and Mid-Life Biochemistry

Mood changes were observed and chronicled using questionnaire below. The results are reported together with observable data from laboratory serum analysis and menses. Women were asked all ten questions during each session. Some of the questions are historical in nature (especially #10) and were not repeated each session.

1. Are you anxious? (irritable, short tempered)
2. Are you depressed? (lethargic, low energy)
3. Where are you in your menstrual cycle?
4. Are you having trouble sleeping?
5. Are headaches an issue?
6. Do you have a general sense that life is working?

7. Are you sexually interested?
8. Do you have obsessive thoughts?
9. Do you exhibit compulsive behavior?
10. Do you have a history of difficult periods, PMS, cramps?

Sample Size and Research Methodology

The sample sizes for this study were necessarily small, due to the high cost of obtaining the laboratory serum analyses, lack of funding for the study and most importantly, the individualized care given to the subjects. The research methodology adopted was that of "single case" study. After an extensive review of quantitative and qualitative research methods, it was decided that this was the correct approach for this research with its emphasis on biochemical individuality.

Laboratory Analysis of Plant-Derived and Synthetic Progesterones

Progesterone from two sources was analyzed by infrared spectroscopy at the research laboratory of Dr. Dwight M. Smith, University of Denver, Department of Chemistry and Biochemistry.

Plant-derived Progesterone: Pharmaceutical grade progesterone was obtained from the Women's International Pharmacy, Sun City, AZ, where it was extracted from a soy base.

Synthetic Progesterone, or Medroxy-progesterone Acetate: This progesterone was pharmaceutical grade "Provera", generic name Medroxyprogesterone acetate. Provera is a progestin prescribed by doctors to treat menstrual disorders. It was obtained by prescription in the form of 2.5-mg tablets produced by the Upjohn Company, Kalamazoo, MI.

Clinical Trial Results

Group 1: Focus Group: 2 women (the author being one of them) were studied intensively for 26 (Subject 2) to 29 months (Subject 1). Subject 1

Data were collected on subject 1 forty-four times from September 1996 through February 1999 and are presented in **Figure 1**, below, **Figure 2**, p. 4 and **Figure 3**, p.4. The data correlated with the symptoms as follows. The initial test, drawn from serum in September of 1996 at mid-cycle or ovulation, indicated very high levels of estrogen to 641.8 picograms/milliliter (pg/ml), high for non-pregnant women in their early to mid forties should be 443 pg/ml, and that is considered high. The progesterone was at 5.1 nanograms/milliliter (ng/ml), while the objective high should have been in the 15-25 ng/ml range. To mediate the carcinogenic, and other, effects of heavy estrogen the level of progesterone would have needed to be upwards of 20 ng/ml.

This was a startling revelation; that it really is about the interaction of the levels not just the objective levels themselves. The data were examined by several physicians, notably Dr. Wilson (OBGYN) and Dr. Whitcomb. One question concerned the difficult pregnancy for subject 1. Heavy estrogen dominance is a major factor in extreme nausea during pregnancy In fact, the subject was hospitalized with hyperemesis, extreme nausea and unable to eat. These levels are now suspected to respond favorably to high doses of natural progesterone to mediate the estrogenic impact. This is now known to be a major factor in post-partum depression and is often countered with natural progesterone.[1]

After seeing this, the conjecture was developed to look at the emotional impact on peri-menopausal women of low progesterone levels. It is suspected that high estrogen levels produce an imbalance in the system that aggravates or causes symptoms of tension and anxiety. Subject 1 felt unusually irritable at mid-cycle when low progesterone was first established. This emotional pattern was observed subsequently every time the imbalance manifested itself in serum levels.

A protocol was established after first

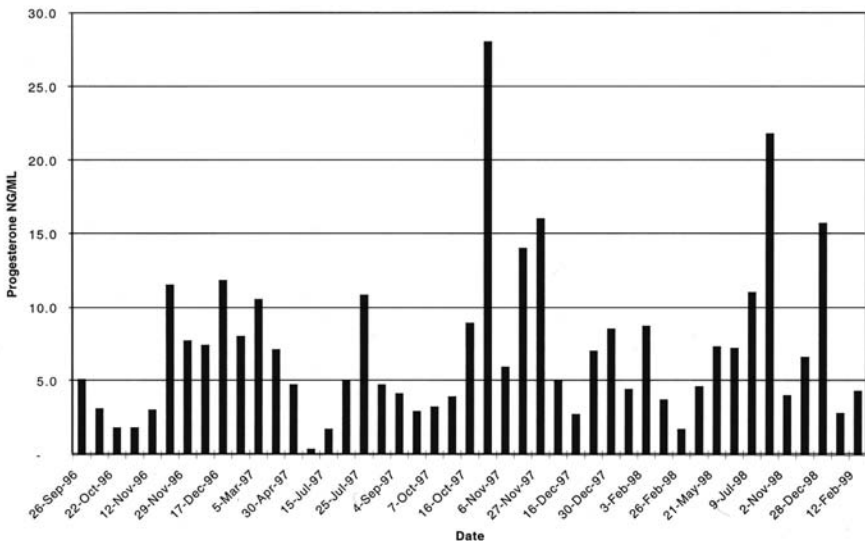Figure 1. Progesterone Levels: Subject 1.
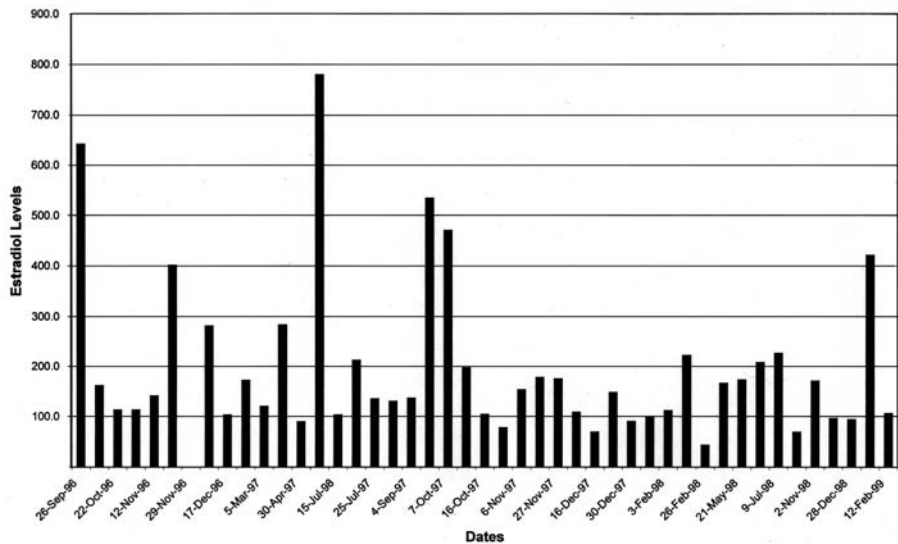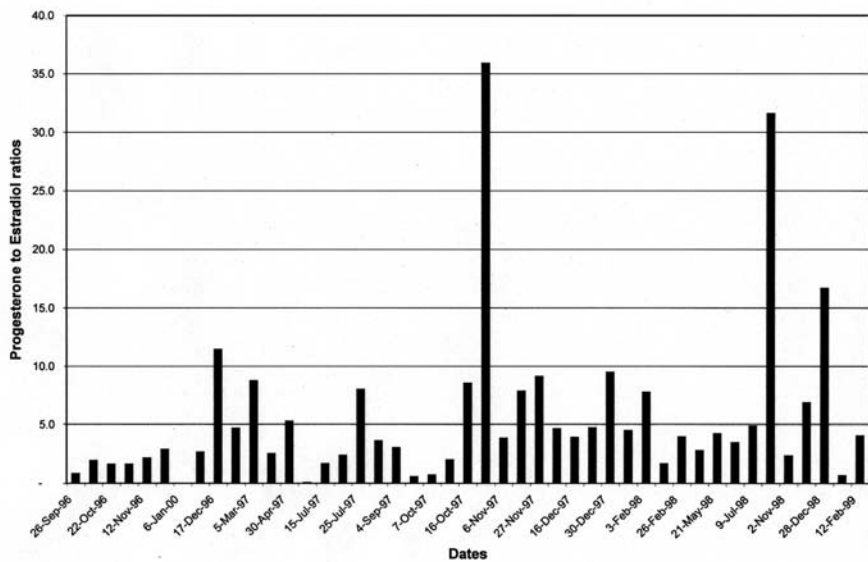
Figure 2. Estradiol Levels: Subject 1.

Figure 3. Progesterone to Estradiol Ratio: Subject 1.

levels were observed: 100 mg. of pure (natural) progesterone cream applied transdermally, (through the skin) bid. This amount was increased if the feeling of intense irritability persisted. From the beginning the serum levels responded to the progesterone increase by general elevation in progesterone, and a dramatic, over time decrease in elevated estrogen. Specifically, one month later the estradiol, which is the most commonly used form of estrogen for measuring overall serum values, was down to 400.3 pg/ml and the progesterone had climbed to 11.5 ng/ml. This trend continued for a year. Subject one continued to experience increased feelings of well-being. The objective measurements correlated strongly with the interpretive aspects: there were continued and generally improved feelings of calmness and factors related to the neuroinhibitory receptors in the brain, the part of the mid- brain which regulates anxiety. This is where progesterone does its neuro-chemical work. Estrogen works primarily on the serotonin pathways that affect depression, not anxiety as much as the benzodiazapine receptors do.

Subject 2:

Data were collected on subject 2 twenty-five times from June 1996 through August 1998 and are presented in**Figure 4,** below, **Figure 5,** p. 6 and **Figure 6,** p.6.

Subject 2 was extremely interesting: Her feelings of increased well being correlated with the use of natural progesterone over time, however there is an important distinction between her symptoms and those of subject 1. When her estrogen was high, and her progesterone levels were low, she would exhibit extreme rage, followed by conciliatory, self-defeating demeanor the next day. As time went by and her progesterone levels came up, she no longer became as depressive following periods of anger and rage, which is how she manifested anxiety.

Interestingly for subject 2, all her adult life she had thought she was prone to significant depression. She had been treated with psychotropic medications, specifically Paxil and Prozac with little relief. After treatment with natural progesterone for fifteen months, from October of 1996 until December of 1997, she finally felt really well premenstrually for the first times in years. This has continued but with some variations.

Subject 2, it is now believed, had so much rage that after she calmed down she could focus on the depression that has lurked for years under the surface. Interestingly, subject 2 decided to try medication for short term for depression and now the drug (Paxil) is helping her. When she is

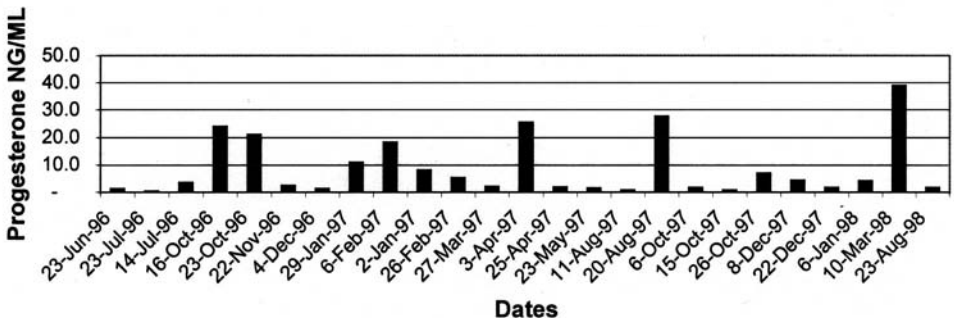Figure 4. Progesterone Levels: Subject 2.

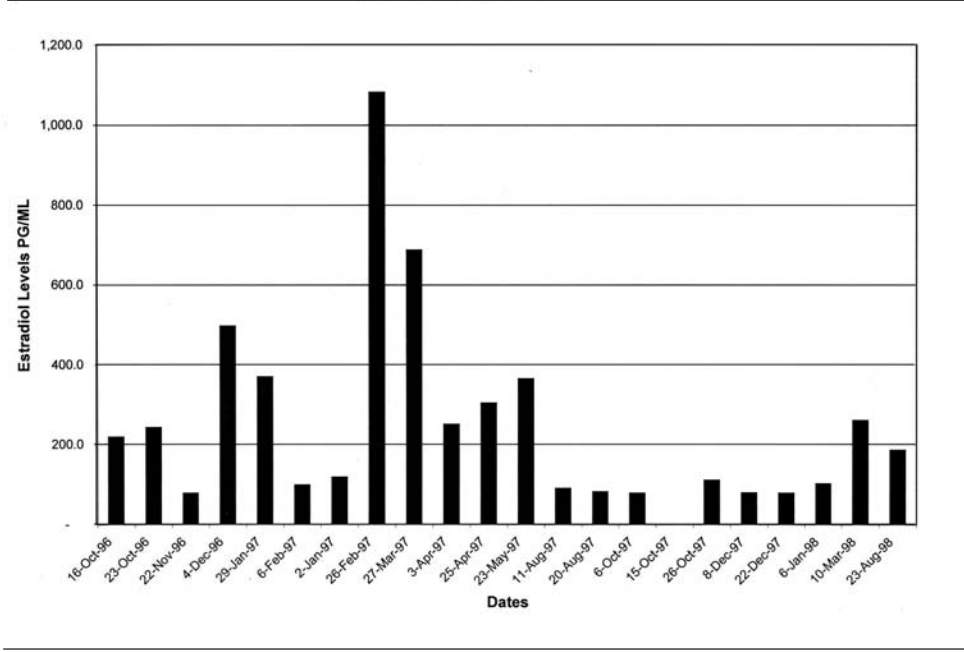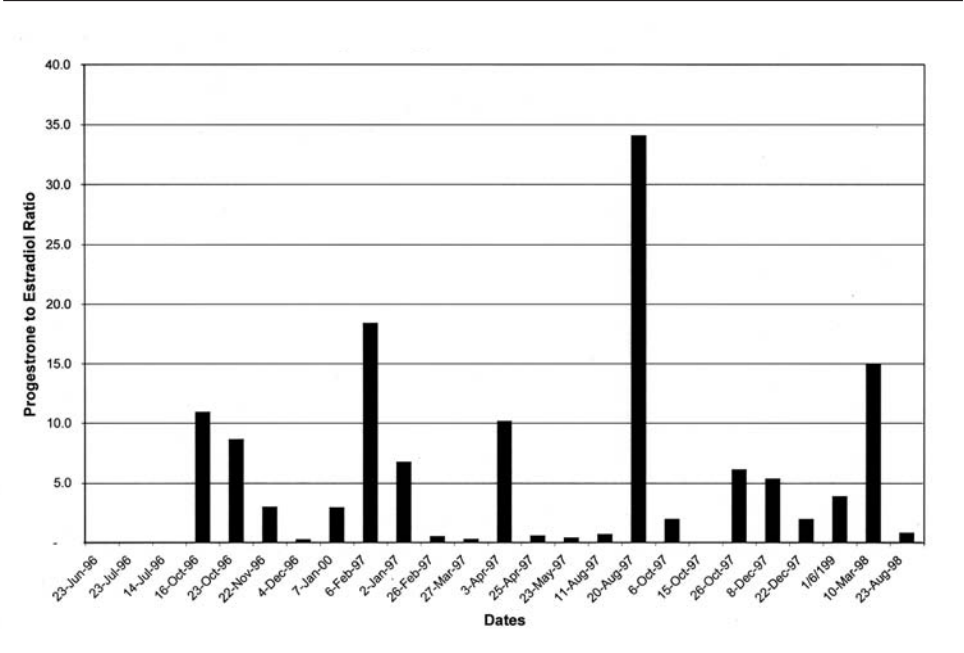**Figure 2.** Estradiol Levels: Subject 1.

Figure 2. Estradiol Levels: Subject 1.

ready, I would like to see her work with more biochemical options with depression as well as for the anxiety.

Her progress has been slower than that of subject 1 but significant. She reported feeling best at times when progesterone levels came up at least to 4 ng/ml, and estrogen levels decreased below 100 pg/ml.

On December 8, 1997 she began a period of well being which was the best she had felt in many years. At that time the estrogen showed 79 pg/ml and the progesterone was at 4.2 ng/ml.

In the time following the pilot study, the author has found that when anxiety-prone women get the progesterone serum level above 15/mg /mL, true calmness sets in.

A major contrast with these two subjects is that subject 2 tends to cry easily when she is tense and angry. She also likes alcohol, very much, which subject 1 can "take or leave."

The general improvement in mood over two years for each woman has been remarkable. The amino acid treatments provide overall biochemical improvement in equilibrium; however pre-menstrual tension continued to run high in both these women, albeit with somewhat distinct manifestation of symptoms. After the introduction of micronized progesterone, in the form of transdermal progesterone cream, pre-menstrual tension has essentially been obliterated.

It is important to note that the six women in this phase of the study were initially given over the counter 1.6% progesterone cream. This is "micronized progesterone" in the physiologic doses recommended by John Lee, MD. Physiologic dosing refers to doses comparable to those that occur naturally in the female body. Four of the women reported improvement in premenstrual and menstrual cramping. Three women reported less brain fog and cognitive dysfunction. Only one of the women in the initial dosing group reported any improvement in neuro-chemical or emotional symptoms of mood biochemistry. This was a two-month introductory phase before the clinical trial began. The mood changes occurred when there was a discernible shift in the progesterone/ estrogen ratios as discussed from figure three, these data carried the same implications in the broader study as well. In case after case, as serum levels of progesterone rose with continued treatment, the mood improved in these women. The broad implications are being observed because we are seeing this trend show up in many more subjects not in the original study but being seen at our clinic.

Each woman in the two-year study reported that in the week prior to menstruation the cream would disappear (transdermal absorption) within fifteen seconds, as contrasted with earlier in the post-ovulatory phase often taking two to three minutes. This was observed by each subject independently. The vehicle for transdermal uptake is penetration of micronized progesterone through the skin. This is consistent with the observations of K. Dalton as reported in The British Medical Journal.[2] This would indicate very active receptor site availability.

Group 2: Estrogen Dominance

Six Women Showing Tendencies Toward "Estrogen Dominance:" With the second group of women, the focus was on correlating aspects of mood dysfunction with hormonal imbalance and other criteria as well. These women were being treated for general mood symptoms of mid-life with amino acid therapy. We then expanded their protocol as we began this study to include natural hormones. The first group of six women was prone to anxiety and tension, more than depression. Most had made considerable progress on amino acid therapy alone and improved considerably when natural progesterone was added to these protocols.

These women were informed about being part of this study and signed release

forms. They were delighted to have this tracking of mood symptoms because generally they felt that their various mood symptoms were dismissed as being peripheral instead of perhaps generative of other problems with their health.

The women discussed below are representative of the broader study in that their symptoms typify estrogen dominant patterns.

The following women were anxiety type patients who turned out to be estrogen dominant. Serum levels were measured at, or post, ovulation two to three times over a nine month to one year period.

The first woman, D, came in because of severe PMS. This refers to Pre-Menstrual Syndrome that can involve headaches, bloating, significant mood changes, tension and sometimes rage. Her gynecologist had treated her with various drugs, including one to suppress testosterone; strangely, progesterone was not on the list. Her initial serum progesterone at mid-cycle showed negligible progesterone at 1.4 ng/ml, not nearly enough to mediate the high levels of estrogen. Her marriage was failing because she was so irritable and she could not control it. She was one of those miracle cases; we have several of these now. She said the first two week trial of using progesterone was dramatic–she felt like herself for the first time in years. Initially we gave her 1.6% over the counter progesterone. As her menstruation date approached some symptoms intensified, notably irritability, and so we then ordered 6% progesterone from Women's International Pharmacy, compounded to our specifications. She has continued to thrive. I am continuing to follow her progress.

M is another anxious and irritable woman. Her husband said he felt she was obsessing about his mid-life depression and was using that to avoid looking at her own extreme hyper-irritability. In fact, she was increasingly angry with her husband for being depressed. According to her, he had

no right to be depressed since her family had done so much for him financially. In fact, this was part of his problem. Her problem was that she was so tense she could think of no one but herself, her mind raced and she talked incessantly. Interestingly, her mother, while much older, had similar personality traits and had been on Premarin with Provera, synthetic progesterone for years. Her mother had negligible progesterone serum levels even after years of being on synthetic methyl progesterone.

M reported irregular periods, which started after the birth of her fourth child, She also had post-partum depression that increased after she weaned her last baby. This is an often over-looked time of post-partum problems.

She reported incredible mood swings; her husband said she was simply angry, not seeing his perspective. She felt overwhelmed and the slightest trigger could send her into a rage. Also, three of her four children had symptoms of hyperactive behavior or attention deficiency, one of them is severe.

The subject was given "Anxiety Control"[3] to use as a base nutrient. This is a 24 hour neuro-transmitter support formula for anxiety, based on utilizing glutamine and glycine to "walk" GABA across the blood-brain barrier. This helped calm her rage. Adding 10% natural micronized progesterone two weeks before her next menstrual cycle began has helped her distressed mood during that time even more. Although she has been a difficult woman to work with, she is showing improvement. She had initial mid-cycle progesterone levels of 0.4 ng/ml with an increase to 5.2 ng/ml over four months.

The third woman, B, in this phase of the study demonstrated the classic symptoms of the estrogen dominant female more than any other I have seen. She had negligible (not measurable) luteal progesterone of less than 0.4 ng/ml, which is essentially off the scale. She came to our of-

fice hysterical saying she could not calm down and was having recurrent panic attacks daily. She reported obsessive thought processes that were traumatic for her. She was extremely high strung and felt she has "no containment" for these virulent emotional swings that upset her a great deal. She felt out of control with panic, rage, and anger, mostly directed toward her husband.

Subject four, Q, was the extreme of a group of three women, with cases five and six showing similar symptoms, but not as severe. So, in telling about Q, I see these other two cases mirrored but their behavior was not as extreme. Q would show no impulse control when angry and has wounded people irrevocably, or so it would seem. Q was given high doses of the neuro-inhibitors GABA and Taurine at 750 mg. and 1000 mg. for three months. This helped her enormously in reducing her feelings of panic. Cases five and six were given similar nutrients but in smaller doses. During the luteal phase, particularly the week prior to menstruation, the rage use to intensify. She has experienced steady improvement since she started using 100 mg. of natural progesterone six times a day. This is the dose that keeps her sane. Over time, if she is able, this might be reduced. In the meantime there is absolutely no harm in this protocol and it may help save her marriage. The other two subjects in this subgroup responded to 300 mg. and 400 mg. during this time period. Again, they were quite similar but less severe cases.

Group 3: Estrogen Deficiency

The women showing low levels of estrogen are fewer in our perimenopausal group by about 5 to 3. Most of the women in this age range tend toward estrogen dominance. This group is important here primarily as a statistical control: there are conjectures made by people working in the field that all women should throw out estrogen and only use progesterone. This

is not solid science. Theoretically, in the cascade of hormones, progesterone will convert to estrogen eventually. However, in some women this happens very slowly and sparingly.

Women in peri-menopause in this group show a great deal of consistency in their symptoms. There was little to no anxiety and no panic attacks were reported. The general complaint was depression and fatigue. Autoimmune illnesses seemed to be pervasive in this group. Three of these women had autoimmune indication in their blood. One had significant lupus, one had chronic fatigue and one had fibromyalgia. Lack of motivation was another factor. Four women reported that "it is an effort to do anything." They were generally not in touch with their anger because they were too tired. Researchers have suggested that women who can not express anger introject emotions, or turn them inward. My associate, Dr. Whitcomb, speculates that these women are prone to degenerative disease, often-autoimmune illnesses.

The women in this control group were followed by the gynecologist we work with and used Bi-Est, a natural estrogen, made from soybeans comprised of 80% estriol, the overlooked yet safest, non-catechol, non-conjugated estrogen, and 20% estradiol to closely mimic the woman's estrogen. This was always accompanied by natural progesterone to counter the potentially carcinogenic effects of even the safest estrogens.

Laboratory Analysis Of Plant-Derived And Synthetic Progesterones

Pure samples of Medroxyprogesterone acetate (MPA) (Figure 8, p.11) and plant-derived progesterone (Figure 7, p.11) were analyzed by infrared spectroscopy at the research laboratory of Dr. Dwight M. Smith, University of Denver, Department of Chemistry and Biochemistry. Infrared spectroscopy was utilized instead of our originally intended vapor phase chromatography/mass

spectroscopy because the molecular weight of the progesterone molecules was too high for vapor phase chromatography. Both of these processes are used to establish the structure of molecules.

The data transformed certain previously held beliefs about the chemical structures of these molecules. Figure 8 shows the structure popularly known as medroxy-progesterone acetate and referenced as MPA in the cardio-vasospasm study.[4] The spectral analysis revealed that it has a distinctly different configuration than has been assumed, even by pioneers in medicine using natural progesterone, such as in the writing of Dr. John Lee, Dr. Jesse Hanley and others. Natural progesterone is conventionally distinguished from synthetic by the emphasis on additional methylation; both synthetic and natural progesterone contain methyl groups. Figure 8, the synthetic molecule of Provera, in this case, shows great distinction from Figure 7 not in methylation but in hydroxylation and the presence of acetate.

Figure 7 shows the structure commonly referenced in the popular literature on alternatives to synthetic hormones and differs because of the lack of hydroxylation, not just the lack of a methyl group as commonly stated.

The synthesis of androgens (male hormones) starts with the hydroxylation of progesterone at C-17. The side chain consisting of C-20 and C-21 is cleaved to produce androstenedione, an androgen. Testosterone, another androgen, is formed by the reduction of the 17- keto group of androstenedione. Androgens contain 19 carbon atoms. Estrogens are synthesized from androgens by the loss of the C-19 angular methyl group and the formation of an aromatic A-ring.[5]

Summary and Conclusion

This research addressed two areas: first, a clinical research project focused on the moods and biochemistry of women at mid-life, and second; a laboratory analysis of synthetic and plant derived progesterone.

Clinical Study

The clinical study addressed three specific questions (see page 1 above), which are reiterated with the results below:

1. Does a deficiency of progesterone affect anxiety patterns in mid-life or perimenopausal females? The clinical study found that a deficiency of progesterone is clearly implicated as a primary factor in mid-life anxiety patterns. As women increased the uptake of natural progesterone at 100 mg/dose, serum progesterone levels increased and seemed to mediate excess estrogen. These changes in serum levels clearly correlated with the qualitative input given by these women on questionnaires and in personal interviews.

2. Is mid-life anxiety in women connected to low progesterone levels or estrogen dominance? Mid-life anxiety in women correlated with anxiety being more extreme during the luteal phase, or latter two weeks of the menstrual cycle. Even though objectively this is when there is a gradual natural increase in progesterone production. The data showed that there is often too much estrogen to be mediated by the body's available progesterone.

3. Are amino acids and/or plant-based hormones effective in the treatment of anxiety? In the follicular phase, or first two weeks of the menstrual cycle, women predisposed to anxiety patterns reported significant improvement in their well being while taking neuro-inhibitory amino acids alone (GABA, Taurine, Glutamine). However, as the ovulatory peak of estrogen dominance started, and moved into the luteal phase, these effects diminished, even in women using physiologic, low doses of progesterone. When neuro-inhibitory amino acids were used in conjunction with pharmaceutical grade, natural progesterone, women thrived and reported

Figure 7. Infrared spectroscopy analysis of Pure samples of plant-derived progesterone.
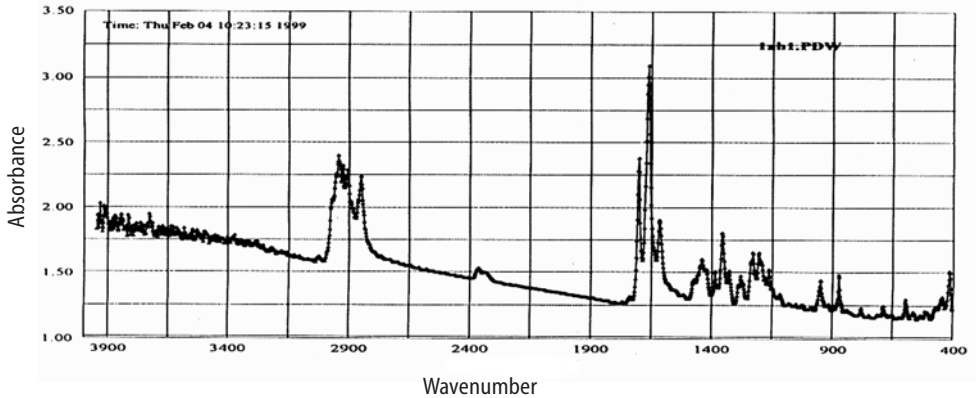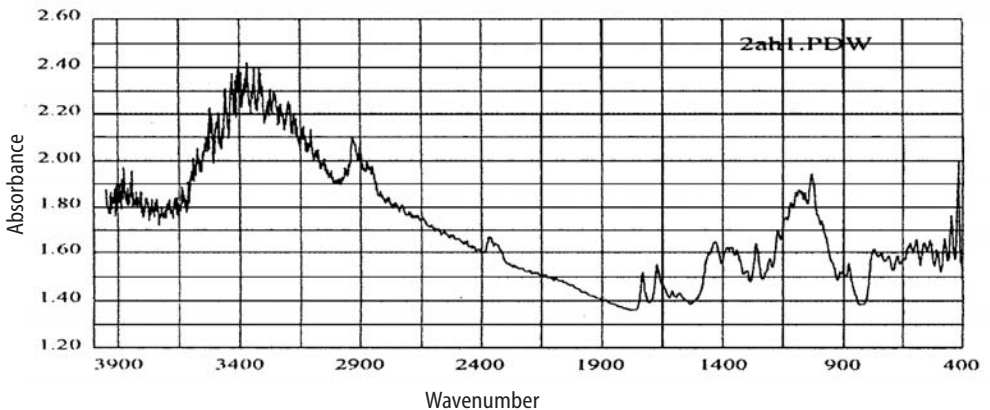

Figure 8. Infrared spectroscopy analysis of Pure samples of Medroxyprogesterone acetate (MPA).

greatly increased calmness, even during the normally difficult pre-menstrual phase

Laboratory Analysis of Synthetic and Natural Progesterone

The laboratory analysis of synthetic and plant derived progesterone revealed significant differences in their structures and revealed discrepancies between the published and ac-tual structure of the synthetic progesterone, Provera. The primary distinction between natural progesterone and its synthetic counterpart turned out not to be in methylation, but rather in hydroxylation and the presence of acetate in the synthetic molecule.

Discussion

Clinical Results of this Study: Peri-menopausal women balanced over time and then developed some other symptoms that were analogous with drops in estrogen precipitated by the leveling effects of progesterone and by the fact of peri-menopause itself. This became intriguing in the context of the premise that good science is frequently counter-intuitive.[6,7]

These data infer that the women in the study were in treatment for various symptoms that are usually considered constitutive of anxiety (many of these symptoms had been assessed as clinical anxiety by a physician or psychologist).

We used the National Mental Health Association clinical depression checklist to gather more information.

The women with anxiety were treated with neuro-inhibitory nutrients, specifically amino acids such as GABA or Taurine. While there was initial improvement on amino acid therapy alone, the improvement diminished in the premenstrual two-week period of time. We therefore conjecture that the calming effect of progesterone might be because it augments the effect of GABA, and acts like a benzodiazapine itself.

Over the initial six months the results were consistent and extraordinary. The data suggest that the incidence of anxiety decreased markedly when women were using trans-dermal natural progesterone cream that largely bypasses liver function. Affirmative answers to question 1: "Are you anxious?" decreased over time congruent with the use of natural progesterone.

These women being assessed quantitatively were also questioned qualitatively during the time of blood studies. This component was extremely useful, as there are many gradations in the perceptual experience of anxiety, from mild discomfort or feeling nervous to panic episodes.

Specifically, in the two women followed over four years, there were parallel responses in terms of "changes in mood." Similar results were seen in the expanded shorter study with the larger group of estrogen dominant women. The basis of this study could be expanded into an outstanding larger study if the funding becomes available.

The evidence points toward the premise that in anxiety prone women, when progesterone levels are low relative to estrogen, these subjects feel tense and irritable, and exhibit other criteria of general anxiety. Relief of these symptoms is generally seen when progesterone is measured at 8-15 ng/ml. The mood changes were qualified as follows. As the progesterone levels rose gradually, most symptoms of acute anxiety disappeared. Chronic symptoms took longer to dissipate, although they too diminished over time. The subjects also reported that if they were not diligent about using progesterone, symptoms recurred. As each woman was viewed individually, required progesterone levels varied, based upon their biochemical individuality. These fluctuations are reflected in the data.

Most of this inquiry developed over the realization of the disturbing errors in perception I see being applied in traditional medicine, specifically the danger of molecules such as medroxy-progesterone acetate. Those issues are obvious to the reader by now, and are addressed thoroughly in this paper and my related work.

A less obvious finding, which emerged later in this work for me, was the lack of pure scientific information by those supposedly invested in this alternative discourse. I refer here to the recent work of John Lee. He is the pioneer in the use of natural progesterone. Lately, while I have always maintained that he is myopic I have found him misguided. In his zealousness to promote the use of his "physiologic" dose of progesterone I see women getting led astray. He insists that women need only small amounts of progesterone to get relief for their peri-menopausal symptoms.

This study strongly contradicts Dr. Lee's approach. The women seen repeatedly

reported that the changes in mood happened congruent with elevated serum hormone levels of progesterone, usually accompanied by a drop in high estrogen levels! Early in our research these changes did not occur at physiologic doses (as promoted by Dr. Lee) or when low dose progesterone was used at 1.6%.

I conjecture that the petrochemical estrogens in the environment, as well as E1 and E2 found in animal foods, elevate our own estrogenic response significantly. These catechol estrogens are a definitive link to many cancers in men as well as women. Therefore due to higher than normal exposure to estrogenic substances today, the increased proportions of progesterone are necessary to mediate the toxicity by blocking receptor activity. The head of Women's International Pharmacy has come to similar conclusions to mine from years of research and is excited about the importance of this study.

This is a powerful study of mood changes at mid-life and beyond. This research has profound implications on the connection of hormonal changes and amino acid biochemistry. Further, in women of peri-menopausal age there are substantial data linking women who are estrogen dominant, i.e. top heavy in estrogen relative to progesterone, and irritability patterns and/or rage. Women tend to get more irritable and men tend more toward intense anger. There now appears to be a biological basis to this, as well as a neuro-chemical one. There are data to support the premise that estrogen itself is neuro-excitatory. High levels of estrogen may predispose certain women to high levels of anxiety, including panic attacks.

Dr. Ray Peat[8] has been looking at this neuro-excitatory pattern for years. Dr. John Lee has also discussed this,[9] and we have great regard for his work. However, we are finding that for neuro-chemical purposes, higher doses are required to alter the neurotransmitters in the brain and nervous sys-

tem than are available from Dr. Lee's physiologic amounts. These data are corroborated by researchers at Women's International Pharmacy and other compounding pharmacies. These pharmacies make hormones from substances that occur naturally, and mimic the way our own bodies manufacture hormones. The primary source for these hormones is soybeans. This is in sharp contrast to traditional hormone replacement therapy, which is dependent on conjugated, unnatural estrogens and progestins or synthetic progesterone.

Natural progesterone has neuro-inhibitory or calming effects similar to GABA, taurine and other neuro-inhibiting or calming amino acid precursors to brain chemicals. The neurotransmitters are the chemical languages that one part of the brain speaks to another domain. People who have trouble focusing, concentrating, or remembering how to do something are deficient in these biochemical messengers.

We now believe that there is too much estrogenic effect on women and men of the wrong type of estrogen, E1 and E2, due to environmental and dietary factors. These estrogens contribute to many cancers which are estrogen fed, and have a significant impact on the brain.

That is why many biochemists are horrified at the return to an emphasis on animal based or Paleolithic types of diets advocated in certain pop nutrition books today. We believe there is a connection between the anxiety epidemic and the high estrogen in animal foods.

We do concur with one aspect of Enter the Zone by Dr. Barry Sears,[10] that people eating too many carbohydrates may become insulin resistant. We advocate a plant-based diet high in proteins. The return to animal based eating does not make sense for mid-life women because animal food, especially chicken and beef contain the wrong estrogens. This is the basic premise of Dr. Neal Barnard, head of the Physicians Committee on Responsible

Medicine, and the author of several fine books. In addition, we urge readers to read or reread *Diet for A New America.*[11]

Implications For Future Study: This is a pilot study; already the impact has been enormous in helping some women solve the riddle of mid-life anxiety. This is the first study to look at correlations between fluctuations in estrogen/progesterone ratios and amino acid and neuro-transmitter levels that are genetically and biologically driven.

My vision is to expand this into a context for working on other mood disorders in as significant a manner. I want to use the data to continue the research into a foundational study on "Alternatives to Ritalin" for children. In terms of social impact, this is imperative. How can we tell children not to take drugs when we try drugs[12] in one form or another to solve every problem?

Human beings must come to peace with the dance of being human. We each bring a rich and varied history to life. This history becomes the fabric of who we are. Similarly, we each bring a biochemical blueprint and a biologically driven make-up to life. To quote Heidegger: 'We are thrown to be a certain way."[13] We must learn to integrate our psychology into who we are, not attempt to eradicate symptoms which can, and often should, become powerful teachers. I do not mean to imply that people should suffer needlessly. There is a series of fine lines here. Nevertheless, we must start to evolve into a species that takes responsibility for our individual lives, including our health, with proper guidance.

To close, I shall quote Caroline Myss from "Anatomy of the Spirit" where she states: "One cannot be a victim and be consciously creating one's own reality at the same time."[14]

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New genetic marker of risk for breast cancer discovered

Memorial Sloan-Kettering Cancer Center (MSKCC) and the National Cancer Institute
http://www.mskcc.org/ 4-Mar-2008

An international group of investigators led by scientists at Memorial Sloan-Kettering Cancer Center (MSKCC) and the National Cancer Institute has identified a new genetic marker of risk for breast cancer.

Women with this DNA variation are at a 1.4 times greater risk of developing breast cancer compared to those without the variation. The findings are to be published online on March 3, 2008 in the journal Proceedings of the National Academy of Sciences.

"These results are exciting because they point us to new molecular pathways that may be associated with breast cancer," said the head of the research team and the study's senior author, Kenneth Offit, MD, MPH, Chief of the Clinical Genetics Service at MSKCC.

The study used a methodology called genome-wide association mapping, which looks at genetic variations across the entire genome that alter the individual building blocks of DNA makeup. These alterations may occur more frequently in individuals who have certain types of disease than in carriers without such disease. In this study, a new gene locus, a specific place on a chromosome where a gene is located, was associated with breast cancer risk. That gene locus is on the long arm of chromosome 6.

"These research findings are of great interest because of the method of genome- wide association used to discover this new locus as well as others in recent months," said Bert Gold, PhD, a Staff Scientist at the National Cancer Institute in Frederick, MD., and first author of the current study.

While the risk associated with this genetic marker is much lower than that of BRCA genetic mutations for example, this discovery will increase the understanding of the genetic variants that contribute to breast cancer.

Researchers used samples largely from MSKCC, but also from other sites in the US, Canada, and Israel. Participants were all of Ashkenazi (Eastern European Jewish) ancestry. The study used a three-phase design centered on 249 families with multiple cases of breast cancer and no mutations of the BRCA genes.

"This newly identified genetic marker will not have any immediate clinical implications or impact on current screening guidelines for familial breast cancer," said Dr. Offit. "As such, a test for these markers is not available to the general public and these tests should be performed only as part of research studies."

Dr. Offit's research team is now confirming that this risk marker is observed in other populations, and is studying possible changes in two genes in the chromosome 6q region.

New way to assess a woman's risk for invasive breast cancer

http://www.ucsf.edu/   6-Mar-2008

Researchers at the University of California, San Francisco have developed a way to quickly estimate a woman's risk for invasive breast cancer.

The new model, based on a measure of breast density that is already reported with the majority of mammograms today, is the first to be validated across multiple ethnic groups living in the United States.

The model could one day be used to help calculate a woman's risk for breast cancer each time she has a mammogram, providing her with a realistic sense of her likelihood to develop breast cancer in the future.

"Breast density is the strongest risk factor after age for developing breast cancer," said lead author Jeffrey Tice, MD, assistant professor in the Department of General Internal Medicine at UCSF. "Unfortunately, there is no model currently available to clinicians for assessing breast cancer risk that includes this important risk factor. The model we have
created could be a useful tool to improve breast cancer screening and prevention efforts and to help women better understand the magnitude of risk."

The findings are reported in the March 4, 2008 issue of The Annals of Internal Medicine.

The standard and most commonly used risk assessment model available to clinicians today is the Gail model, a previously validated breast cancer risk assessment tool that is primarily based on non-modifiable breast cancer risk factors. The Gail model was developed and validated in Caucasian women only. Tice and colleagues from UCSF and the University of Washington designed a new model that estimates predicted incidence of
invasive breast cancer by using breast density, age and ethnicity. The estimates are then adjusted for family history of breast cancer and history of breast biopsy (whether or not a woman had undergone a previous biopsy for a suspect lump or lesion).

"Physicians are used to calculating their patients' risk for heart disease, but we don't routinely do it for breast cancer," said Tice. "Breast density classification in women, assessed during screening mammography, is already part of a routine clinical practice. Our goal was to develop a simple and useful model incorporating this data which
estimated a woman's risk for invasive breast cancer in multiple ethnic groups."

The research team used data from more than one million women who visited screening mammography sites across the United States between 1996 and 2003. Model calibration was assessed by calculating the ratio of expected cases of breast cancer to observed cases of breast cancer. Calibration, according to the study, assesses how closely the number of
women in whom the model predicts that breast cancer will develop matches with the actual number of women in whom breast cancer is diagnosed. An observed ratio of 1.0 would indicate perfect calibration.

Study results showed the model they developed was well calibrated and reasonably accurate across risk factor subgroups. After five years of follow-up, the observed rate of invasive breast cancer was 1.40 percent (8,784 cases of cancer among 629,229 women) compared to the expected rate created by the model of 1.41 percent. However, the model slightly underestimated breast cancer rates in younger women (age 40-44) and underestimated cancer rates among Asian and Hispanic women.

"We found that a model that incorporates mammographic breast density can estimate a woman's risk for invasive breast cancer and is convenient enough that it could be incorporated into routine breast cancer screening," said Tice. "Primary care physicians could use it to calculate a woman's five year risk of developing breast cancer."

Tice warns, however, this is not the definitive model for breast cancer risk assessment and that it is unlikely a single model would be able to address all needs in breast cancer risk assessment. Some women will benefit from genetic counseling and screening, other women will require more detailed risk factor assessment, he adds, and this new model, like the Gail model, had only modest ability to discriminate between women overall who will develop breast cancer and those who will not.

One of the more surprising and unexpected findings in this study, according to Tice, was how poorly the Gail model performed in this population of ethnically diverse women. When the researchers compared their model to the Gail model, they found the Gail model was poorly calibrated and underestimated the number of breast cancers by 12 percent. This was particularly true for African American women in whom the Gail model under-predicted the number of breast cancers by 45 percent. The researchers hypothesize this may be because the Gail model was developed and validated in Caucasian women only.

"The most important finding of this study is the accuracy of the model across multiple ethnic groups," added Tice. "This is strong evidence that supports the inclusion of race and ethnicity in any risk assessment tool created in the future.

Cruciferous vegetables may lower risk for breast cancer
http://www.mc.vanderbilt.edu/npa   10-Mar-2008

When your mother told you to eat your vegetables it appears that maternal wisdom had a scientific basis.

Researchers with Vanderbilt-Ingram Cancer Center and the Shanghai Cancer Institute in China have discovered a possible link between a diet rich in certain vegetables and a decreased risk for breast cancer. The study appears in the March issue of the American Journal of Clinical Nutrition.

Corresponding author Jay Fowke, Ph.D., assistant professor of Medicine at Vanderbilt-Ingram, said 3,035 women diagnosed with breast cancer were identified through the Shanghai Cancer Registry. They were closely matched with 3,037 women randomly chosen from the general population there. The women filled out questionnaires about their diet, including consumption of

cruciferous vegetables like Chinese cabbage, bok choi and turnips. Americans typically eat more broccoli, kale and cauliflower in the cruciferous vegetable family.

"Cruciferous vegetables contain some compounds that may have a cancer-inhibitory effect," explained Fowke. "Here we were able to identify a group of women who seem to particularly benefit from a high intake of these vegetables."

While there was only a small positive relationship between a diet high in these vegetables and a reduction in breast cancer risk for the overall study population, there was a striking risk reduction - 50 percent - among women with a certain genetic profile. Researchers identified three forms of the GSTP1 genotype among the cancer patients: Ille/Ile, Ile/Val and Val/Val.

"Women who consumed more of these cruciferous vegetables and who also had the Val/Val genetic polymorphism had a lower breast cancer risk. So we cautiously interpreted this as diet being a factor that may reduce the impact of genetic susceptibility in overall breast cancer risk," said Fowke.

The Vanderbilt-Ingram researchers focused on cruciferous vegetables because they contain two chemicals called isothiocyanates and indole-3-carbinol which may affect carcinogenesis by triggering cell death or by shifting estrogen metabolism. Studies by other researchers have suggested cruciferous vegetables may reduce the risk of lung, stomach, colorectal and bladder cancers.

"We have known for some time that certain foods, like soy foods, appear to interfere with the development of breast cancer because they contain plant estrogens," said Fowke. "The protective effect from cruciferous vegetables in this study was certainly suggestive of a risk reduction, but researchers need to replicate this finding in other studies."

Scientists were able to isolate the specific genetic profile linked with a positive dietary impact because the women in the study submitted DNA through blood and cheek cell samples. Wei Zheng, M.D., Ph.D., professor of Medicine at Vanderbilt-Ingram is the principal investigator for the Shanghai Breast Cancer study.

"The Shanghai Breast Cancer Study is one of the largest and most comprehensive epidemiological studies conducted to date for this common cancer," according to Zheng. "We have published over 100 research papers in this study addressing a large range of significant issues related to the etiology and survival of breast cancer. The results reported by Dr. Fowke may have significant implications in breast cancer prevention."

While women in this study answered questionnaires about their diets, researchers want to measure more precisely the intake of cruciferous vegetables. To aid in future studies they are collecting urine samples which contain biomarkers for the beneficial chemicals.

Authors for this paper include: Sang-Ah Lee, Wei Lu, Chuangzhong Ye, Ying Zheng, Qiuyin Cai, Kai Gu, Yu-Tang Gao, Xiao-ou Shu and Wei Zheng.
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New device - combination PET and MRI scanner

10-Mar-2008
http://www.ucdavis.edu/

Two kinds of body imaging - positron emission tomography (PET) and magnetic resonance imaging (MRI) - have been combined for the first time in a single scanner.

MRI scans provide exquisite structural detail but little functional information, while PET scans -- which follow a radioactive tracer in the body -- can show body processes but not structures, said Simon Cherry, professor and chair of biomedical engineering at UC Davis. Cherry's lab built the scanner for studies with laboratory mice, for example in cancer research.

"We can correlate the structure of a tumor by MRI with the functional information from PET, and understand what's happening inside a tumor," Cherry said.

Combining the two types of scan in a single machine is difficult because the two systems interfere with each other. MRI scanners rely on very strong, very smooth magnetic fields that can easily be disturbed by metallic objects inside the scanner. At the same time, those magnetic fields can seriously affect the detectors and electronics needed for PET scanning. There is also a limited amount of space within the scanner in which to fit everything together, Cherry noted.

Scanners that combine computer-assisted tomography (CAT) and PET scans are already available, but CAT scans provide less structural detail than MRI scans, especially of soft tissue, Cherry said. They also give the patient a dose of radiation from X-rays.

The photomultiplier tubes used in conventional PET machines are very sensitive to magnetic fields. So the researchers used a new technology -- the silicon avalanche photodiode detector -- in their machine. They were able to show that the scanner could acquire accurate PET and MRI images at the same time from test objects and mice.

New study links breast cancer to hormone therapy

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TORONTO - The first Canadian study of its kind is adding to a growing body of international evidence suggesting that the use of hormone replacement therapy may raise the risk of breast cancer.

However, some doctors counter that such studies do not prove a cause-and-effect association between taking hormones and the onset of breast cancer, and stress there could be many other factors playing a role in the development of the disease.

The study by the Canadian Cancer Society found there was a significant decrease in the rate of new breast cancers among post-menopausal women between 2002 and 2004 -- coinciding with a huge drop in the use of hormone replacement therapy, or HRT.

Many Canadian women stopped taking hormones in 2002 after a massive U.S. clinical trial -- the Women's Health Initiative -- suggested the risks of taking HRT outweighed the benefits. That study suggested taking hormones appeared to increase the risk of breast cancer, heart attack, stroke and blood clots in the lungs.

Following release of that data, the proportion of Canadian women taking HRT began falling dramatically. In 2004, just five per cent of women aged 50 to 69 were on the drugs, compared to 13 per cent in 2002.

"The drop in breast cancer incidence was fairly significant," said lead author Prithwish De, an epidemiologist with the Canadian Cancer Society. "We saw a 10 per cent drop in the incidence rate of breast cancer from 296 per 100,000 women to about 278 per 100,000."

At the same time, the rate of mammography did not change and so was not a factor, say the authors, whose report was published online Thursday in the Journal of the National Cancer Institute.

De said the study is the first national analysis of HRT use and breast cancer incidence rates in Canada. It follows a similar U.S. study published in 2007, which found disease rates plunged in 2003, the year after millions of American women stopped taking hormone pills.

"It certainly gives a Canadian perspective to the growing international evidence around the association between breast cancer incidence and HRT," he said. "It also supports the Canadian Cancer Society position (that) women should avoid using HRT for any reason other than managing severe menopausal symptoms."

Yet, the study also turned up an interesting finding that has led some to question the validity of the HRT-breast cancer link.

The decline in breast cancer incidence continued until 2005, dropping to 266 per 100,000 women, after which the annual rate began to rebound -- rising to about 279 per 100,000 in 2006 -- even though hormone therapy use was virtually unchanged from 2002.

Dr. Jennifer Blake, chief of obstetrics and gynecology at Sunnybrook Health Sciences Centre in Toronto, said after examining the study data that "it's very hard for me to be convinced."

"There's just so many unknowns," said Blake, who was not involved in the study. "I think we have to be very clear when we look at these studies that we're not able to make any kind of a causative relationship. All you're saying is that there's an observation of an association and you don't have any way of knowing whether they're related."

She said there are many risk factors for breast cancer -- including obesity and the age at which a woman has her first period, first child and goes into menopause. As well, the risk of developing the disease increases with age.

The short window between the drops in hormone use and breast cancer incidence also raises a red flag, said Blake, since many studies have shown that it takes about five years from discontinuing hormone therapy for breast cancer risk to return to "baseline."

Dr. Christine Derzko, an obstetrician and gynecologist at St. Michael's Hospital in Toronto, said the rebound in incidence in 2006 cannot be ignored.

"We have to ask the question why was that. We have to ask was the drop before that real," said Derzko, pointing out that it takes about seven to 10 years for a breast tumour to develop to detectable levels from the rise of the first cancerous cell.

"If you stop a hormone, why should all this disappear?"

The theory is that taking hormones can make small but undetectable breast cancers grow, and when hormone therapy is stopped, then growth stops, she said. "It's less obvious, so the pickup rate (by mammogram or physical examination) may be less."

"Subsequently ... a few years later, eventually just on their own steam, they have grown to the point where they are seen," she said.

While hormone is not the only answer to dealing with menopause, Derzko said menopausal women should discuss with their physicians what is appropriate for treating hot flashes and other unpleasant and disruptive symptoms.

"We are not uncomfortable with providing hormones to women who are between 50 and 60 ... immediately in the post-menopausal period," she said. "Their consideration of hormone therapy should remain on the list."

"But it's incumbent on them and us as physicians to make sure we are watching them, that we're making sure their mammograms are done."

Read more: http://www.ctvnews.ca/new-study-links-breast-cancer-to-hormone-therapy-1.556274#ixzz2Jz9PpE6E

Organophosphate Pesticide Exposure and Neurobehavioral Performance in Agricultural and Nonagricultural Hispanic Workers

Joan Rothlein,[1] Diane Rohlman,[1] Michael Lasarev,[1] Jackie Phillips,[2] Juan Muniz,[3] and Linda McCauley[3]

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Our understanding of the health risks of farmworkers exposed to pesticides in their work and home environments is rapidly increasing, although studies designed to examine the possible neurobehavioral effects of low-level chronic pesticide exposure are limited. We measured dialkyl phosphate urinary metabolite levels, collected environmental dust samples from a subset of homes, obtained information on work practices, and conducted neurobehavioral tests on a sample of farmworkers in Oregon. Significant correlations between urinary methyl metabolite levels and total methyl organophosphate (azinphos-methyl, phosmet, malathion) house dust levels were observed. We found the neurobehavioral performance of Hispanic immigrant farmworkers to be lower than that observed in a nonagricultural Hispanic immigrant population, and within the sample of agricultural workers there was a positive correlation between urinary organophosphate metabolite levels and poorer performance on some neurobehavioral tests. These findings add to an increasing body of evidence of the association between low levels of pesticide exposure and deficits in neurobehavioral performance. *Key words:* biomarkers, farmworkers, neurobehavior, occupational health, organophosphates, pesticides. *Environ Health Perspect* 114:691–696 (2006). doi:10.1289/ehp.8182 available via *http://dx.doi.org/* [Online 23 January 2006]

In recent years, there has been increasing concern regarding the widespread use of pesticides in agricultural communities and potential impacts on public health. In the 1990s in the United States, some 2.5–5.0 million agricultural workers were exposed to organophosphate insecticides (Das et al. 2001). Scientific field investigations have focused on delineating the extent of exposure and potential health effects in agricultural and nonagricultural communities. Detectable levels of pesticides have been reported in home dust, primarily in families residing in agricultural areas (Bradman et al. 1997; McCauley et al. 2001; Quandt et al. 2004; Simcox et al. 1995). Bradman et al. (1997) found that diazinon and chlorpyrifos concentrations in house dust tended to be higher among farmworkers than among nonfarmworkers. Others have reported higher levels of pesticides in house dust in homes that are located closer to fields (Quandt et al. 2004) and in housing with larger numbers of farmworkers (Azaroff 1999; Lu et al. 2000; McCauley et al. 2001). After-work hygiene practices, such as leaving work boots outside and changing promptly from work clothes, have also been found to affect pesticide levels in the homes of farmworkers (McCauley et al. 2003).

Studies have also documented the presence of biologic markers of pesticide exposure in adults and children in agricultural communities (Arcury and Quandt 2003; Azaroff 1999; Loewenherz et al. 1997; O'Rourke et al. 2000) and differences among levels of exposure in residents of agriculture and nonagricultural communities. Although the association between acute exposure to pesticides

and neurotoxic effects is well known (Lotti 2000), the potential effects of chronic low-level exposure are less well established (Alavanja et al. 2004).

Neurobehavioral (NB) test batteries have frequently been used to examine NB effects of acute pesticide exposure in adult working populations. Individuals with histories of toxic exposures to organophosphates have shown a consistent pattern of deficits on measures of motor speed and coordination, sustained attention, and information processing speed (Reidy et al. 1992; Rosenstock et al. 1991; Savage et al. 1988; Steenland et al. 1994; Wesseling et al. 2002). Fewer studies have examined the effect of long-term, low-level exposure to pesticides on nervous system functioning, but NB changes have been reported in sheep farmers (Stephens et al. 1995), greenhouse workers (Bazylewicz-Walczak et al. 1999), tree fruit workers (Fiedler et al. 1997), and farmworkers in Florida (Kamel et al. 2003). These studies have found deficits in measures of sustained attention, information processing, and motor speed and coordination. An examination of a group of cotton pesticides applicators in Egypt presumed to have high exposures, found a broad range of deficits, including visual motor speed, verbal abstraction, attention, and memory (Farahat et al. 2003).

Although these studies represent increasing knowledge regarding the association between pesticide exposure and neurologic health end points, few studies have reported the association between environmental exposures, biomarkers of exposure, and neurologic performance. We conducted an investigation of

migrant farmworkers in Oregon and included measures of environmental exposure, biomarkers of exposure, and NB performance.

In this study, we hypothesized that *a*) significant correlations would be found between the amount of organophosphate residues in house dust and the levels of organophosphate metabolites in urine of adult farmworkers living in an agricultural community; *b*) the NB performance of Hispanic immigrant farmworkers exposed to organophosphates would be lower than that observed in a nonagricultural Hispanic immigrant population when controlled for demographic factors such as age and education; and *c*) within the agricultural workers, there would be a positive correlation between urinary organophosphate metabolite levels and poorer NB performance.

Materials and Methods

Target communities. The agricultural community at Hood River is a productive and long-established agricultural community primarily producing pears and apples and located along the Columbia Gorge, approximately 100 km east of Portland, Oregon. The farmworker population in Hood River tends to consist of newly arrived and more permanent Hispanic residents who live in cabins, trailers, single- and multifamily homes, or apartments that are located in or alongside orchards. Harvesting of tree fruit begins in August and extends through October. The study was conducted as a partnership with the Oregon Child Development Coalition, which is the grantee for the Oregon Migrant Head Start Program. Ninety-six farmworkers were recruited by

community members of the Migrant Head Start program in Hood River. All attendees at parent meetings at Migrant Head Start who had a child enrolled in a Migrant Head Start program and were currently working in the orchards, fields, and nurseries were invited to participate. Participants ranged from 20 to 52 years of age and were all originally from Mexico. Some of the parents first arrived in the United States in 1970, and some parents had just arrived for the first time in 1998. After the families were recruited, they were scheduled for a home visit, at which time questionnaires were administered and dust samples collected.

To compare performance on NB tests, we recruited immigrant workers from Newport, a tourist coastal town with little agriculture in Lincoln County, Oregon. The Hispanic work-force in Lincoln County consists of immigrant workers who are employed primarily by the local hotels and tourist industry. Most of these individuals came to Oregon 6–8 years earlier after they were solicited in Mexico to work in the Oregon fish canning industry. When the canning business declined, these workers remained in Newport to work in hotels and restaurants. They were recruited for this study by a community member with the support and partnership of the Hispanic community organizations Centro de Ayuda and Un Paso Adelante. The individuals were recruited one on one through word of mouth, community contacts, and neighborhood grocery stores. Workers were eligible to participate in the study if they had not worked in agriculture during the previous 3 months (including nurseries, farms, and fruit packing plants), were 18–50 years of age, had not attended school in the United States other than English-as-second-language classes, did not use a computer at work, and had never had an acute illness associated with pesticide exposure.

All biologic samples and NB assessments of both farmworkers from Hood River and the control group from Newport were conducted in the evenings after their workday. Participants were paid an incentive for participating in this study. The study protocol and procedures for informed consent were reviewed and approved by the Oregon Health and Science University Institutional Review Board (protocol 4216) and complied with all applicable requirements of the U.S. regulations.

Data collection. Spot urine samples for pesticide metabolite analysis were collected from farmworkers once during the summer and again in the fall. Samples were collected from each farmworker at the Migrant Head Start center in the evening after work just before taking the NB tests. Samples were labeled, and transferred on ice to the Oregon Health and Science University analytical laboratory. Urine specimens were adjusted to pH 3.0, aliquoted into test tubes, and stored at –20°C until extraction and analysis.

House dust samples were collected from a subsample of 26 farmworkers' homes during the same week as collection of the first urine sample. Azinphos-methyl [AZM; trade name Guthion; Chemical Abstracts Service (CAS) No. 86-50-0], chlorpyrifos (CAS No. 2921-88-2), and phosmet (trade name Imidan; CAS No. 732-11-6) are used to control orchard pests such as coddling moth and are applied two to four times from May through August in the Hood River community. We timed our collection of home dust samples and urine samples to coincide with the middle of the growing season and the time that pesticide spraying applications were being applied to crops in the Hood River community. Dust samples were collected using a high-volume, small surface sampler (HVS3) as described in Lewis et al. (1994) and Simcox et al. (1995). All samples were collected from carpeted areas in the most commonly used play area for their children and living area for adults. All samples were collected in Teflon bottles (E.I. Dupont Company, Wilmington, DE) by vacuuming a measured area on a rug or carpet designed to collect an approximate 5-g sample. Samples were transported to the lab in a refrigerated cooler and stored below –20°C before analysis.

Both the farmworkers and control participants received NB testing in the evenings after work. Controls were tested once in spring and the farmworker participants were tested twice, in the summer and fall. Although our farmworker and control populations were recruited from two different communities, we assembled similar NB testing environments in both the Newport and Hood River testing sites. Testing stations were set up by using panel dividers to partition tables into different stations. Each station contained a computer, response unit, and headphones. Instructions on how to complete the computerized tests were given in Spanish. Four to six participants were tested at one time in air-conditioned meeting rooms. NB tests were selected from the Behavioral Assessment and Research System (BARS). BARS is a computerized test system that employs both written and spoken instructions (both via computer) (Rohlman et al. 2003). To minimize the adverse impact of working on an unfamiliar device such as a computer keyboard, a durable response unit with nine buttons is placed over the keyboard (pictured in Anger et al. 1996). The BARS test instructions have been translated into Spanish, recorded, and digitized. Instructions were written in Spanish on the screen and also delivered simultaneously through headphones. The eight BARS tests include measures of psychomotor functioning (finger tapping, simple reaction time, and progressive ratio) and measures of cognitive functioning (symbol-digit, digit span, selective attention, serial digit learning, and continuous performance).

Laboratory analysis. Dust samples were put through a sieve, extracted with organic solvents, cleaned up using gel permeation chromatography, and analyzed on a Hewlett-Packard (Palo Alto, CA) model 5890 gas chromatograph equipped with a pulse flame photometric detector (OI Analytical, College Station, TX). The organophosphates AZM, diazinon, chlorpyrifos, malathion, methyl parathion, and phosmet were confirmed with gas chromatography (GC)/mass spectrometry mass-selective detector in single ion monitoring mode. Specific methods for sample extraction and sample cleanup, involving filtration and gel permeation chromatography column cleanup and GC analysis, have been previously described (Moate et al. 2002). The limits of detection (LODs) for the six organophosphates were 0.01 µg/gm for diazinon, malathion, chlorpyrifos, and methyl parathion and 0.10 µg/gm for AZM and phosmet.

Urine was analyzed for five dialkyl phosphate (DAP) metabolites: dimethylphosphate (DMP), diethylphosphate (DEP), dimethylthiophosphate (DMTP), diethylthiophosphate (DETP), and dimethyldithiophosphate (DMDTP). Urine samples were prepared for GC analysis according to a modified method of Moate et al. (1999). Aliquots of the samples underwent azeotropic distillation with methanol and evaporation under a nitrogen stream. Sample extracts were then derivatized with 2,3,4,5,6-pentafluorobenzylbromide to convert phosphate acids to esters. Extracted samples were analyzed on a gas chromatograph (Hewlett-Packard model 5890) equipped with a pulsed-flame photometric detector (OI Analytical). The LOD for each of the metabolites was calculated from the instrument response factor corresponding to a concentration having a peak area three times the baseline noise (blank signal). The LODs for the five metabolites were 4.0 ng/mL (0.032 µmol/L) DMP, 2.0 ng/mL (0.013 µmol/L) DEP, 2.2 ng/mL (0.015 µmol/L) DMTP, 1.6 ng/mL (0.010 µmol/L) DMDTP, and 1.6 ng/mL (0.0095 µmol/L) DETP. The average extraction efficiencies of the five metabolites were, respectively, 45, 84, 97, 96, and 93%. Urine samples were also analyzed for creatinine concentrations (milligrams per deciliter), which were determined by the modified Jaffe reaction creatinine procedure No. 555 (Sigma Chemical Company, St Louis, MO).

Quality control/quality assurance. Quality control data generated for each set of urine samples provided an overall assessment of precision, accuracy, and reliability of the method. We conducted spike sample recoveries and urine blank analysis for every set of 12 samples. Urine samples known to contain low levels of

DAP were used for blanks and for spike recoveries. Urine samples were spiked with DAP reference standards varying in concentration from 2 to 50 ng/mL.

Data analysis. We examined the distribution of creatinine and excluded urine samples less than the 5th percentile (26.45 mg/dL) or greater than the 95th percentile (235.5 mg/dL) from further analysis because of concerns of hydration state and metabolic disorders (Loewenherz et al. 1997; Lu et al. 2001). The primary organophosphates applied during the spring and summer season in the agricultural regions under study were AZM and phosmet, both of which break down into the methyl DAP metabolites (DMTP and DMDTP). Therefore, for urine samples, molar equivalent concentrations of the DMTP and DMDTP metabolites were summed to create a measure of thiomethyl DAP concentration. Nondetectable levels of urinary metabolites were replaced by one-half the appropriate LOD before taking the sum.

For house dust samples, residues associated with AZM, phosmet, and malathion (the most common agricultural organophosphates used in the study region) were added together to form a summary measure of pesticides in the house dust. Each of these pesticides metabolizes into the thiomethyl DAPs. Nondetectable levels of dust residues were replaced by one-half the appropriate LOD before taking the sum.

The association between methyl phosphates in house dust and thiomethyl concentrations in urine was evaluated using Spearman's correlation. The difference in urinary thiomethyl metabolites between the first sampling period [summer, time 1 (T1)] and the second sampling period [fall, time 2 (T2)] was evaluated with a Wilcoxon signed-rank test. This test suggested that thiomethyl metabolites from T1 and T2 could be combined for subsequent analyses. Subjects with valid creatinine levels from both sampling periods had their metabolite levels averaged over the two samples; subjects with a valid creatinine level from only one sample contributed metabolite data from only that sample. The partial correlation (Rao 1973) was computed to examine the association between NB test performance from T1 and the averaged thiomethyl metabolite levels after accounting for the effects of sex, age, and education in the subject's country of origin (age and education were treated as continuous variables; sex was a two-level factor). This analysis was conducted for subjects having a valid creatinine level during at least one of the two sampling periods. Differences on each NB test between agricultural (AG) and nonagricultural (non-AG) groups were assessed using multiple linear regression models involving age, sex, years of education in the subject's country of origin, and AG versus non-AG status. Three interactions between AG status and each of

the other predictors were also included in the initial model and simultaneously tested for significance using a partial F-test (Netter et al. 1989). If the test was significant ($p < 0.10$), then each interaction was separately examined and retained in the model if individually significant (again, at the $p < 0.10$ level). Adjusted values reported from the regression model reflect the mean score on each NB test for a 25-year-old subject with 6 years of education in his or her country of origin.

To increase the power to detect effects of exposure between the AG and non-AG population, we derived a summary index of overall NB performance from 11 of the 16 NB test items (digit span forward, digit span reverse, progressive ratio, reaction time, selective attention interstimulus interval, serial digit learning, symbol-digit, preferred-hand finger tapping, nonpreferred-hand finger tapping, alternating-hand finger tapping, and continuous performance percent hits). The items for the summary index were chosen to provide an equal representation of all the multiple measures in the test battery and were chosen before identification of the individual items that were statistically different between the two comparison groups. Measurements for each test were first standardized by subtracting the mean and dividing the difference by the sample SD. Tests involving latency measures had the signs of the standardized measurements reversed to provide consistency with the other measures (higher numbers indicating better performance; lower numbers, weaker performance). We computed the summary index as each subject's average standardized score from the test items divided by the SE. The summary index was similarly analyzed to determine whether significant partial correlations existed with thiomethyl metabolites or if significant differences existed between the AG and non-AG groups.

All p-values are two sided unless otherwise indicated. One-sided p-values were used in cases where the means or correlations were anticipated to follow a prechosen trend. All analyses were performed with R (version 1.9.1; R Development Core Team 2004).

Results

Ninety-nine farmworkers attended the parent meeting at Head Start and were approached

for study participation, with only three declining to participate. Fifty-five controls were recruited for the study, but 10 were excluded because they were working in landscaping or tree planting (forestry), had no formal education in Mexico or the United States, or were not available during scheduled testing times. All farmworkers were immigrants from Mexico, and the controls were primarily from Mexico (two participants were from Guatemala and one unknown). There was no significant difference in the ages of the two groups: farmworkers, 20–52 years of age (mean ± SD = 29.7 ± 6.89); controls, 19–48 years of age (mean ± SD = 27.8 ± 6.19). The control group averaged 1.1 years more education than the farmworkers ($p = 0.04$; 95% confidence interval, 0.026–2.2 years more). The percentage of males in the two groups was not significantly different ($p = 0.33$). The mean time since first arrival in the United States was 9.8 years for farmworkers and 7.3 years for controls.

Pesticide residue in house dust. Our pesticide data included carpet dust samples from 26 farmworkers' homes. Data on the six organophosphates we analyzed are reported in Table 1. At least one of the six organophosphates was detected in each of the homes. Phosmet, with a median detected concentration of 4.40 μg/g, was detected in 25 of the 26 homes (96%). AZM was detected in 18 of the 26 homes (69%) but had a higher detected median concentration (5.30 μg/g). Neither of these organophosphates is registered for residential use, and spray records from local growers in the area reported orchard application of phosmet and AZM two to four times from May through August. The organophosphates chlorpyrifos, parathion, malathion, and diazinon were detected at frequencies between 62 and 92% but at median detectable concentrations several times lower than found for AZM or phosmet.

Urinary metabolite levels. The two sampling periods with farmworkers provided a total of 172 urine samples (93 samples at T1, 79 samples at T2). We analyzed the urinary metabolites for all samples, but two samples were of insufficient volume for subsequent creatinine analysis. The distribution of creatinine levels in the remaining 170 samples was

Table 1. Organophosphate pesticides detected (μg/g) in farmworker housing in Hood River, Oregon, 1999 ($n = 26$).

	Diazinon	Methyl parathion	Chlorpyrifos	Malathion	Phosmet	AZM	Combined total[a]
No. detected (%)	20 (77)	16 (62)	24 (92)	21 (81)	25 (96)	18 (69)	
LOD	0.01	0.01	0.01	0.01	0.01	0.10	
Minimum	0.01	0.01	0.01	0.05	0.16	0.30	0.57
Mean ± SD	0.31 ± 0.23	0.38 ± 0.60	0.20 ± 0.24	0.38 ± 0.40	5.2 ± 4.1	5.9 ± 4.5	10 ± 6.5
Median	0.31	0.06	0.13	0.18	4.4	5.3	9.4
Maximum	0.72	1.9	1.2	1.4	22	16	26

[a]Sum of six organophosphate pesticide residues; nondetects replaced by half the LOD before summation.

examined, and urine samples less than the 5th percentile (26.45 mg/dL) or greater than the 95th percentile (235.5 mg/dL) were excluded from further analysis because of concern about hydration state and metabolic disorders. This restriction reduced to the number of valid urine samples to 84 and 68, respectively, for T1 and T2; 88 subjects had valid urine samples for at least one of the two sampling periods.

DMTP was the most commonly quantified organophosphate metabolite (Table 2). The percentage of the complete sample above the LOD was 97 and 100%, respectively, for T1 and T2. When computed for samples with valid creatinine levels, the median concentration of the combined thiomethyl metabolites (DMTP, DMDTP) was 0.43 μmol/L at T1 (n = 84) and 0.48 μmol/L at T2 (n = 68); the median increased to 0.56 μmol/L when data from the two time periods were averaged together and the sample was broadened to include subjects with at least one valid creatinine measurement (from T1 or T2).

No significant differences were found between the median concentrations of thiomethyl metabolites from the two periods (p > 0.20 for both DMTP and DMDTP, Wilcoxon signed-rank test). Males tended to have higher levels of DMTP and combined thiomethyl metabolites at both time points compared with female farmworkers.

Correlation of home dust samples and urinary metabolite levels. Twenty-three of the 26 carpet dust samples had pesticide residues that could be paired with the combined molar concentration of thiomethyl metabolites (DMTP and DMDTP) from valid urine samples. A moderate but significant positive correlation existed between these 23 pairs of methyl pesticides (sum of AZM, phosmet, and malathion) and their metabolites (micromoles per liter) (Figure 1). The impact of the three uppermost points observed in Figure 1 is reduced when summarized using Spearman's correlation (r_s = 0.47, one-sided p = 0.013).

Correlation between NB performance and urinary metabolite levels. Ninety-two farmworkers (51% male) and 45 controls (60% male) completed NB tests. NB performance was compared with the combined thiomethyl metabolites (DMTP + DMDTP) averaged

across the two urine samples. After adjusting for age, sex, and years of education, poorer performance on five NB tests was associated with higher levels of the average combined thiomethyl metabolites: selective attention latency, symbol-digit latency, preferred-hand finger tapping, alternating-hand finger tapping, and continuous performance hit latency (Table 3).

Comparison of NB performance between farmworkers and controls. Overall, non-AG controls performed better on 12 out of 16 NB measurements compared with 92 farmworkers (Table 4). Multiple linear regression was used to compare performance on the NB tests between the AG and non-AG groups while controlling for age, years of education in country of origin, and sex. Interactions between these three covariates and employment in agriculture may have also been included if significant (p < 0.10).

Significant interactions between agricultural status and the covariates were found on the serial digit learning test [AG × age: $F(1,122)$ = 3.96, p = 0.049; AG × sex: $F(1,122)$ = 4.28, p = 0.041], the symbol-digit test [AG × education: $F(1,127)$ = 4.20, p = 0.043], and preferred-hand finger tapping [AG × sex: $F(1,129)$ = 4.73, p = 0.031]. Table 4 contains scores for AG and non-AG groups adjusted to reflect the mean response for a 25-year-old individual with 6 years of education; results are shown separately for each sex in cases where a significant AG × sex interaction was found. Interactions involving agricultural status and either age or education are shown in Table 5. Scores on the symbol-digit (latency) tests improved (i.e., decrease) significantly with increasing education for both groups, but the AG group showed greater benefit from each additional year of education. On the serial digit learning test, the two groups have linear trends that diverge with respect to age, although neither trend is significant. The summary index, derived from 11 of the 16 NB tests, also exhibited an AG × sex interaction [$F(1,129)$ = 6.51, p = 0.012].

Discussion

To the best of our knowledge, this is the first study to report a correlation between occupation, pesticide residues in house dust, biologic indicators of exposure, and effects on

NB performance. Although the sample is limited to a migrant farmworker population in Oregon, the results link multiple points on the exposure–health effects pathway that underlies studies of environmental and occupational exposure and health. We have previously reported that the pesticide residues in the house dust of farmworker homes in Hood River exceed those found in homes in other agricultural and nonagricultural regions of Oregon (McCauley et al. 2001). Farmworkers are exposed to pesticides from both work practices and living in housing close to agricultural fields. Although not measured in the present study, we have previously reported that the average distance of farmworker housing to agricultural fields is 15 m in the Hood River community (McCauley et al. 2001).

Application dates in the spray records from orchards in the Hood River neighborhoods surrounding the homes of the participants in this study indicate that applications of phosmet and AZM in this region occurred within 1 week of our dust sample collection. The variability of levels of pesticide in household dust according to season and spraying activity has not been well established and would be difficult to ascertain in most agricultural communities because field-specific information on product name, amount applied at each location, and the crop type are not available. At this time, only six states have legislation requiring extensive reporting of pesticide use, including individual grower use.

The correlation found between environmental contamination and levels of urinary metabolites is a further example of a take-home pathway of pesticide exposure and points to the importance of home hygiene practices to decrease take-home exposures (Coronado et al. 2004; McCauley et al. 2003). Overall, the correlation found is impressive given that current pesticide levels in house dust are merely a marker of exposure history
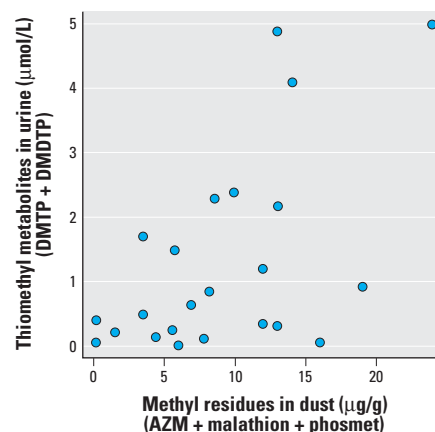
Figure 1. Scatter plot of combined methyl residues found in dust versus thiomethyl metabolite concentration in urine (n = 23 pairs). Spearman's correlation is 0.47 (one-sided p = 0.013).

Table 2. Urinary metabolite levels (μmol/L) in farmworkers at T1 and T2.

		Percent detect[a]		Mean ± SD[b]		Median[b]	
	LOD	T1 (n = 93)	T2 (n = 79)	T1 (n = 84)	T2 (n = 68)	T1 (n = 84)	T2 (n = 68)
DMTP	0.015	97	100	0.63 ± 0.79	0.67 ± 0.67	0.34	0.35
DMDTP	0.010	74	95	0.34 ± 0.69	0.54 ± 0.88	0.09	0.12
DETP	0.0095	34	33	0.04 ± 0.12	0.02 ± 0.03	0.00	0.00
DMTP + DMDTP[c]	—	—	—	0.97 ± 1.40	1.21 ± 1.46	0.43	0.48

—, not defined for combined quantities. Nondetects were replaced by one-half the LOD before computing summary statistics. [a]Complete sample. [b]Valid urine samples only. [c]DMTP + DMDTP for T1 and T2 combined with at least one valid urine sample (n = 88): mean, 1.01 ± 1.08; median, 0.56.

and not a direct measure. We have previously reported in a small sample of growers in Hood River a significant correlation between self-reported hygiene practices and levels of pesticides in home dust (McCauley et al. 2003). It is important that health education messages to this community include information on measures that growers and farmworkers can take to prevent home contamination (Coronado et al. 2004; McCauley et al. 2003; Thompson et al. 2003). Of particular importance is the removal of work shoes outside of living areas, changing from work clothes and showering upon arriving home, frequent mopping of hard floor surfaces, and steam cleaning carpets when appropriate. This was a community-based participatory research study, and all the study results have been shared with advisory board members and farmworkers in the community. We also have reported on the development and dissemination of a training video that emphasizes take-home pesticide contamination and the importance of home hygiene practices (Napolitano 2002).

Among individuals of similar age and education, we found that nonagricultural adults performed better on most of the NB measures that we included in our testing protocol. Measuring NB performance in immigrant, non-English-speaking populations and obtaining comparable comparison groups are always scientific challenges. Participants from both groups in this study had been residing in the United States for comparable periods of time and had similar years of education. Both groups emigrated from similar areas of Mexico. Both groups tend to maintain strong ties with the recently immigrated families within their community. Most important, the Latino community organizations within the state informed the researchers on the similarities of these two groups and how the tourism workers would be an appropriate comparison population to the farmworkers. Both groups are very similar in their engagement in low-paying jobs such as agricultural work, housekeeping or janitorial services for the hotel industry, or restaurant workers in a tourism community.

These findings add support to a growing body of evidence of NB changes in occupational groups chronically exposed to pesticides (Bazylewicz-Walczak et al. 1999; Fiedler et al. 1997; Kamel et al. 2003; Stephens et al. 1995). A pattern of poorer performance among farmworkers was observed on most measures in our test battery. The performance measures that we found to be associated with agricultural work are also measures that have been shown to be associated with low-level, chronic exposures to pesticides, including sustained attention, information processing, and motor speed and coordination.

In research conducted to date, measuring differences in performance on highly specific NB tests has been the most common methodologic approach. The correlation between the types of deficits seen, replication of specific deficits across studies, correlation with animal models, and the toxicologic effects of these chemicals is no doubt of extreme importance. However, Alavanja et al. (2004) and Heyer et al. (1996) point out the utility of grouping results of NB tests as a tool in interpreting findings because it will increase the power to detect effects of exposure in epidemiologic investigations. We found the summary index useful in discerning differences in exposure groups and sex effects. We did, however, construct the summary index *a priori* to reflect components of all the major areas being tested. Selective attention latency and continuous performance latency were not part of the summary index but showed a significant correlation with the levels of urinary metabolites. Future methodologic investigations of the utility of a NB summary index are needed.

Interactions have been found between NB performance and demographic variables such as age, education, and sex (Anger et al. 1997). In the present study, the NB summary index score was significantly affected by the sex of the farmworker. The reasons for this effect are unclear. Previous studies of NB performance in farmworkers have generally assumed that observed deficits are a result of pesticide exposure (Kamel et al. 2003), and significant sex effects in humans have not been reported.

Table 5. β-Coefficients from significant interactions in a regression model used to compare NB performance between AG and non-AG groups.

Test (interaction)	β (SE)	p-Value
Serial digit learning (AG × age)		
Non-AG	0.26 (0.17)	0.13
AG	−0.16 (0.12)	0.20
Symbol-digit latency (AG × education)		
Non-AG	−90.87 (40.17)	0.03
AG	−197.52 (33.12)	< 0.01

For each NB test, the coefficient shows the change in average performance for each additional year of age or education.

Table 3. Partial correlations between NB performance and levels of combined thiomethyl metabolites adjusted for age, sex, and education.

Test	Partial correlation	One-sided p-value
Digit span forward[a]	0.122	0.861
Digit span backward[a]	0.144	0.871
Progressive ratio[a]	−0.149[b]	0.088
Reaction time[a]	0.155[b]	0.080
Selective attention trials	−0.120[b]	0.139
Selective attention ISI[a]	0.088[b]	0.214
Selective attention latency	0.251[b]	0.011
Serial digit learning[a]	0.063	0.711
Symbol-digit latency[a]	0.281[b]	0.005
Finger tapping, preferred hand[a]	−0.252[b]	0.012
Finger tapping, nonpreferred hand[a]	−0.132[b]	0.116
Finger tapping, alternating hand[a]	−0.208[b]	0.029
Continuous performance		
% Hits[a]	0.055	0.685
% Correct rejects	0.043	0.647
Hit latency	0.195[b]	0.042
False alarm latency	0.160[b]	0.092
Summary index	−0.184[b]	0.047

ISI, interstimulus interval.
[a]Test is a component of the summary index. [b]Higher levels of metabolites associated with poorer performance.

Table 4. Mean score ± SE for 16 NB tests: adjusted means corresponding to a 25-year-old individual with 6 years of education in his or her country of origin.

Test	AG	Non-AG	One-sided p-value
Digit span forward[a]	4.12 ± 0.17	4.37 ± 0.19	0.10[b]
Digit span backward[a]	3.86 ± 0.19	4.53 ± 0.21	< 0.01[b]
Progressive ratio[a]	600.40 ± 14.53	600.22 ± 16.44	0.50
Reaction time[a]	340.95 ± 10.50	327.77 ± 11.89	0.13[b]
Selective attention trials	450.27 ± 10.03	456.16 ± 11.48	0.31[b]
Selective attention ISI[a]	397.85 ± 13.45	386.19 ± 15.40	0.23[b]
Selective attention latency	323.00 ± 6.64	315.15 ± 7.60	0.15[b]
Serial digit learning[a]			
Male	11.36 ± 1.31	8.36 ± 1.57	0.93
Female	9.33 ± 1.09	11.56 ± 1.66	0.13[b]
Symbol-digit[a]	3034.58 ± 113.74	2973.38 ± 158.38	0.38[b]
Finger tapping, preferred hand[a]			
Male	99.80 ± 2.69	96.88 ± 3.39	0.75
Female	81.68 ± 2.31	90.41 ± 3.60	0.02[b]
Finger tapping, nonpreferred hand[a]	89.22 ± 2.51	90.75 ± 2.84	0.30[b]
Finger tapping, alternating hand[a]	52.25 ± 3.00	46.72 ± 3.42	0.95
Continuous performance			
% Hits[a]	0.90 ± 0.02	0.88 ± 0.02	0.84
% Correct rejects	0.95 ± 0.01	0.97 ± 0.01	0.26[b]
Hit latency	407.82 ± 10.38	396.55 ± 11.63	0.17[b]
False alarm latency	483.36 ± 21.40	494.16 ± 24.88	0.67
Summary index			
Male	1.01 ± 0.32	0.18 (0.38)	0.95
Female	−1.00 ± 0.25	−0.04 (0.39)	0.02[b]

ISI, interstimulus interval. The one-sided p-value tests whether performance within the AG group is lower than within the non-AG group.
[a]Test is a component of summary index. [b]Non-AG performed better than AG.

Several studies of organophosphate exposure in rats have demonstrated differential effects of sex (Dam et al. 2000; Levin et al. 2001, 2002). In this study, male farmworkers tended to have higher levels of methyl metabolites than female workers. These differences could be contributed to cultural, exposure, metabolic, or other yet unidentified factors. It is also important to consider genetic differences in the ability to metabolize organophosphate pesticides (Furlong 2000). Future studies will examine polymorphic differences and their relation to factors in the exposure pathway.

The design of this study has several limitations. Pesticide-specific information cannot be derived from quantitatively measuring the total urinary DAP metabolite levels, and because individual pesticides differ in toxicity, these cumulative measurements cannot be viewed as a measure of total toxicity (Wessels 2003). Furthermore, these biomarkers reflect recent exposure via all pathways over a very short time frame. Pesticide regulation and use are changing, and the pesticides found in home dust will vary according to the types of crops grown in an area. Therefore, similar results may not be found in all agricultural communities. For example, after this study, AZM became less frequently used, and the pattern of pesticides that we found in home dust in the same communities changed. If possible, future studies should include markers of specific organophosphate pesticides rather than DAPs. Reporting systems need improvement so that occupational spray records can be correlated with urinary levels of pesticides.

Urinary metabolites of organophosphate pesticides have a relatively short half-life, and it is unlikely that the performance on the NB tests at a given test session is a temporary influence on performance measured at that given point in time. Rather, the urinary metabolite levels should be considered a marker or approximation of a level of exposure, just as the NB measures are a marker of performance that could change from one testing session to another. So although one could suggest that the differences observed between agricultural and nonagricultural communities is due to pesticide exposure, additional studies are merited.

Conclusions

This study links multiple points on the pesticide exposure–health effects pathway that underlies studies of environmental and occupational exposure and health. Although there have been increasing reports in the literature of the extent of pesticide exposure in agricultural communities, few studies have included markers of potential health effects. The correlation between levels of pesticides in the home and pesticide urinary metabolites points to significant prevention and education implications,

and these messages are important to the farmworker and other agricultural communities. To our knowledge, this study is the first to report a significant correlation between low levels of urinary pesticide metabolites and NB function. The increasing number of reports of NB performance deficits in workers with long-term exposure to pesticides is significant and points to the need for assurance that farmworkers receive mandated pesticide safety training and that occupational biomonitoring extend beyond those individuals who handle and apply pesticides. Finally, improved worker surveillance is needed to allow estimation of the extent of pesticide exposure among a workforce that moves frequently to meet the employment needs of multiple agricultural operations.

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Relation of folates, vitamin B12 and homocysteine to vertebral bone mineral density change in postmenopausal women. A five-year longitudinal evaluation.

Authors: Cagnacci A, Bagni B, Zini A, Cannoletta M, Generali M, Volpe A

Elevation of homocysteine is associated with an increased risk for bone fractures. Whether the risk is due to homocysteine or to the reduced levels of cofactors necessary for its metabolisation, such as folates or vitamin B12, is not completely clear. In this study we wanted to determine whether in postmenopausal women, levels of folates, homocysteine or vitamin B12 are predictive of the rate of vertebral bone mineral density (BMD) change. The study was conducted at the centre for the menopause of our university hospital. Between September 2001 and March 2002, 161 healthy postmenopausal women volunteered for a cross-sectional evaluation of BMD and levels of serum folates, homocysteine and vitamin B12. Women were recalled for a second evaluation of vertebral BMD after about 5 years. Women having used anti-resorptive therapies for more than 1 year were excluded. The analysis was possible in 117 postmenopausal women. The annual rate of vertebral BMD change was independently related to levels of folates (coefficient of regression (CR): 2.040; 95%CI: 0.483, 3.596; p=0.011), and initial BMD values (CR: -0.060; 95%CI: -0.117, -0.003; p=0.040). No significant relation was found between the change of vertebral BMD and homocysteine or vitamin B12. BMD values at the first (r=0.225; p=0.016) and the second (r=0.206; p=0.027) evaluation were related to levels of folates, but not of homocysteine or of vitamin B12. These data suggest an important role for folates deficiency in the vertebral BMD decline of postmenopausal women.

The role of calcium and vitamin D in the management of osteoporosis.

Authors: Rizzoli R, Boonen S, Brandi ML, Burlet N, Delmas P, Reginster JY

The role of calcium and vitamin D supplementation in the treatment of osteoporosis has been extensively studied. The aim of this paper was to reach, where possible, consensus views on five key questions relating to calcium and vitamin D supplementation in the management of osteoporosis. Whereas global strategies that target supplementation to the general population could not be justified in terms of efficacy and health economics, there is a clearer rationale for supplementing patients who are at increased risk of osteoporosis and those who have developed osteoporosis, including those already taking other treatments for osteoporosis. The combination of vitamin D with calcium may be beneficial in terms of efficacy and, perhaps, for optimising adherence.

Vitamin D status, bone mass, and bone metabolism in home-dwelling postmenopausal Japanese women: Yokogoshi Study.

Authors: Nakamura K, Tsugawa N, Saito T, Ishikawa M, Tsuchiya Y, Hyodo K, Maruyama K, Oshiki R, Kobayashi R, Nashimoto M, Yoshihara A, Ozaki R, Okano T, Yamamoto M

Little has been understood about vitamin D status in relation to bone health in Asian women. The purpose of this study was to identify how the serum 25-hydroxyvitamin D (25[OH]D) concentration is associated with bone mass and bone metabolism. This cross-sectional, community-based epidemiologic study was conducted among 600 ambulatory postmenopausal women. The serum 25(OH)D concentration was measured with radioimmunoassay. Other blood biochemical measurements were intact parathyroid hormone and markers of bone turnover, including osteocalcin and type I collagen cross-linked N-telopeptides. Bone mineral density (BMD) of the lumbar spine and right femoral neck were measured with the dual-energy X-ray absorptiometry method using a QDR4500a. The mean serum 25(OH)D concentration was 55.6 nmol/L (SD 14.6). Serum 25(OH)D concentration was linearly associated with BMD of the femoral neck (R(2)=0.020, P=0.003), but not with BMD of the lumbar spine. Odds ratios (ORs) for low BMD (defined as t score < or =-2.5 SD) were calculated for strata defined by 25(OH)D concentration. The prevalence of low BMD of the lumbar spine was significantly higher in the 40- to 50-nmol/L 25(OH)D group (adjusted OR=3.0, 95% CI: 1.3-7.0) compared to the reference group (> or =70 nmol/L). Prevalence of low BMD for the femoral neck was significantly higher in the 30- to 40-nmol/L (adjusted OR=3.6, 95% CI: 1.1-12.1) and the 40- to 50-nmol/L (adjusted OR=7.6, 95% CI: 2.5-23.2) groups compared to the reference group (> or

=70 nmol/L). The mean serum concentration of intact PTH was significantly higher in subjects with serum 25(OH)D <50 nmol/L compared to those with serum 25(OH)D > or =50 nmol/L. The present study suggests that higher serum 25(OH)D concentrations are associated with increased BMD of the femoral neck, and that a serum 25(OH)D concentration of at least 70 nmol/L is needed to obtain high BMD of the femoral neck, and that of at least 50 nmol/L is needed to achieve normal PTH levels and prevent low BMD in home-dwelling postmenopausal Japanese women.

Selected antioxidants and risk of hormone receptor-defined invasive breast cancers among postmenopausal women in the Women's Health Initiative Observational Study.

Authors: Cui Y, Shikany JM, Liu S, Shagufta Y, Rohan TE

BACKGROUND: Few studies have evaluated carotenoids and vitamins C and E in association with the risk of breast cancers defined by estrogen receptor (ER) and progesterone receptor (PR) status. OBJECTIVE: We examined the associations between dietary and supplemental intakes of these nutrients and risk of breast cancers jointly defined by both ER and PR status among postmenopausal women. DESIGN: Our investigation was conducted in the Women's Health Initiative Observational Study. After following 84 805 women for an average of 7.6 y, 2879 incident invasive breast cancer cases had been ascertained, of whom 2509 had receptor data. We used Cox proportional hazards models to assess the associations of interest. RESULTS: Dietary alpha-carotene (highest versus lowest quintile: RR = 0.83; 95% CL = 0.70, 0.99; P for trend = 0.019), beta-carotene (highest versus lowest quintile: RR = 0.78; 95% CL = 0.66, 0.94; P for trend = 0.021), and lycopene (highest versus lowest quintile: RR = 0.85; 95% CL = 0.73, 1.00; P for trend = 0.064) were inversely associated with risk of ER+PR+breast cancer, but not with other breast cancer groups jointly defined by ER and PR status. Total or supplemental beta-carotene and dietary intakes of lutein+zeaxanthin and beta-cryptoxanthin were not associated with breast cancers defined by ER and PR status. Vitamin E (regardless of source) and dietary vitamin C were not associated with breast cancer. However, total and supplemental vitamin C intake had weak positive associations with breast cancer overall. CONCLUSION: Dietary intake of certain carotenoids might be differentially associated with risk of invasive breast cancers jointly defined by ER and PR status among postmenopausal women.

Inverse relation between dietary intake of naturally occurring plant sterols and serum cholesterol in northern Sweden.

Inverse relation between dietary intake of naturally occurring plant sterols and serum cholesterol in northern Sweden.

Authors: Klingberg S, Ellegård L, Johansson I, Hallmans G, Weinehall L, Andersson H, Winkvist A

BACKGROUND: Plant sterols are bioactive compounds, found in all vegetable foods, which inhibit cholesterol absorption. Little is known about the effect of habitual natural dietary intake of plant sterols. OBJECTIVE: We investigated the relation between plant sterol density (in mg/MJ) and serum concentrations of cholesterol in men and women in northern Sweden. DESIGN: The analysis included 37 150 men and 40 502 women aged 29-61 y, all participants in the Västerbotten Intervention Program. RESULTS: Higher plant sterol density was associated with lower serum total cholesterol in both sexes and with lower LDL cholesterol in women. After adjustment for age, body mass index (in kg/m(2)), and (in women) menopausal status, men with high plant sterol density (quintile 5) had 0.15 mmol/L (2.6%) lower total serum cholesterol (P for trend = 0.001) and 0.13 mmol/L (3.1%) lower LDL cholesterol (P = 0.062) than did men with low plant sterol density (quintile 1). The corresponding figures for women were 0.20 mmol/L (3.5%) lower total serum cholesterol (P for trend < 0.001) and 0.13 mmol/L (3.2%) lower LDL cholesterol (P for trend = 0.001). CONCLUSIONS: The present study is the second epidemiologic study to show a significant inverse relation between naturally occurring dietary plant sterols and serum cholesterol. To the extent that the associations found truly mirror plant sterol intake and not merely a diet high in vegetable fat and fiber, it highlights the importance of considering the plant sterol content of foods both in primary prevention of cardiovascular disease and in the dietary advice incorporated into nutritional treatment of patients with hyperlipidemia.

Serrapeptase
Information and Research about Serrazyme

You should consult your Doctor if you are taking any medication.

The natural Chelation-Anti-Inflammatory Serrapeptase has had wide clinical use - spanning over twenty-five years throughout Europe and Asia - as a viable alternative to salicylates, ibuprofen and the more potent NSAIDs. Unlike these drugs, Serrapeptase is a naturally occurring, physiological agent with no inhibitory effects on prostaglandins and is devoid of gastrointestinal side effects.

Uses:
1. Cardiovascular Disease
2. Arthritis
3. Rheumatoid Arthritis
4. Lung Problems
5. Eye Problems
6. Runny Nose and sinusitis problems
7. Sports Injuries
8. Inflammation of any kind

Serrapeptase is a proteolytic enzyme isolated from the micro-organism Serratia E15. This enzyme is naturally processed commercially today through fermentation and was discovered in the silkworm intestine. This immunologically active enzyme is completely bound to the alpha 2 macroglobulin in biological fluids. Histological studies reveal powerful anti-inflammatory effects of this naturally occurring enzyme.

Serrapeptase digests non-living tissue, blood clots, cysts, and arterial plaque and inflammation in all forms. The late German physician, Dr. Hans Nieper, used Serrapeptase to treat arterial blockage in his coronary patients. Serrapeptase protects against stroke and is reportedly more effective and quicker than EDTA Chelation treatments in removing arterial plaque. He also reports that Serrapeptase dissolves blood clots and causes varicose veins to shrink or diminish. Dr. Nieper told of a woman scheduled for hand amputation and a man scheduled for bypass surgery who both recovered quickly without surgery after treatment with Serrapeptase.

Serrapeptase - Technical Information and Studies

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A Potent Proteolytic Enzyme

The inflammatory response is an important mechanism for protecting the body from attack by invading organisms and faulty cells. In the case of immune dis-regulation, the body loses its ability to differentiate between innocuous and potentially dangerous substances. This defective mechanisms results in a wide array of autoimmune diseases such as allergies, psoriasis, rheumatoid arthritis, ulcerative colitis, uveitis, multiple sclerosis and some forms of cancer.

Standard drug therapy for inflammatory-mediated diseases and trauma include steroids and non-steroidal anti-inflammatory agents (NSAIDs). Both classes of drugs offer temporary, symptomatic relief from swelling, inflammation and accompanying pain without treating the underlying condition. These drugs may also be immunosuppressive and cause dangerous side effects. The conscientious physician must weigh the benefits and long-term risks associated with the use of NSAIDs, especially in cases of rheumatoid arthritis. If left untreated, the inflammatory process itself can lead to limitation of joint function and destruction of bone, cartilage and articular structures.

NSAIDs are among the most widely prescribed drugs for rheumatoid arthritis and other inflammatory joint conditions. Their effects are mediated through inhibition of the biosynthesis of prostaglandins. They work by irreversibly blocking cyclooxygenase, the enzyme which catalyses the reactions of arachidonic acid to endoperoxide compounds. The neurological and gastrointestinal side effects of these agents have been reviewed in considerable detail. All of the NSAIDs, with the exception of Cytotec, inhibit prostaglandin El, a local hormone responsible for gastric mucosai cytoprotection. A common side effect from these medications is gastric ulcers. More serious adverse reactions such as blood dyscrasias, kidney damage and cardiovascular effects have been noted. Most physicians rotate among the ten most widely prescribed NSAIDs, as soon as one causes side effects or stops working.

The search for a physiologic agent that offers anti-inflammatory properties without causing side effects may have ended with the discovery of the Serratia peptidase (SP) enzyme. This anti-inflammatory agent is in wide clinical use throughout Europe and Asia as a viable alternative to salicylates, ibuprofen (sold as an OTC in the U.S.) and the more potent NSAIDs. Unlike these drugs, SP is a naturally occurring, physiologic agent with no inhibitory effects on prostaglandins and devoid of gastrointestinal side effects.

SP is an anti-inflammatory, proteolytic enzyme isolated from the microorganism, Serratia El5. This enzyme is naturally present in the silkworm intestine and is processed commercially today through fermentation. This immunologically active enzyme is completely bound to the alpha 2 macroglobulin in biological fluids. Histologic studies reveal powerful anti-inflammatory effects of this naturally occurring enzyme.

The silkworm has a symbiotic relationship with the Serratia microorganisms in its intestines. The enzymes secreted by the bacteria in silkworm intestines have a specific affinity to avital tissue and have no detrimental effect on the host's living cells. By dissolving a small hole in the ~ silkworm's protective cocoon (avital tissue), the winged creature is able to emerge and fly away. The discovery of this unique biological phenomenon led researchers to study clinical applications of the SP enzyme in man.

In addition to its widespread use in arthritis, fibrocystic breast disease and carpal tunnel syndrome, researchers in Germany have used SP for atherosclerosis. SP helps to digest atherosclerotic plaque without harming the healthy cells lining Z the arterial wall. Today, researchers consider atherosclerosis an inflammatory condition similar to other degenerative diseases. Some immunologists are even categorizing atherosclerosis as a benign tumour. Hardening and narrowing of the arterial wall is a cumulative result of microscopic trauma; inflammation occurs in the presence of oxidized lipids.

SP doesn't interfere with the synthesis of cholesterol in the body, but helps clear avital tissue from the arterial wall. It is important to note that cholesterol in its pure state is an antioxidant and a necessary component of the major organ systems in the body. The use of medications, which block cholesterol biosynthesis, may eventually damage the liver and compromise anti-oxidant status of the eyes, lungs and other soft tissues.

While studies with Serrapeptase in the treatment of coronary artery disease are relatively new, a wealth of information exists regarding its anti-inflammatory properties. SP has been used as an anti-inflammatory agent in the treatment of chronic sinusitis, to improve the elimination of bronchopulmonary secretions, traumatic injury (e.g. sprains and torn ligaments), post-operative inflammation and to facilitate the therapeutic effect of antibiotics in the treatment of infections. In the urological field, SP has been used successfully for cystitis and epididymitis.

Double-Blind Studies

SP has been admitted as a standard treatment Germany and other European countries for the treatment of inflammatory and traumatic swellings. In one double-blind study of SP conducted by Esch et al at the German State Hospital in UIm, 66 patients with fresh rupture of the lateral ligament treated surgically were divided in three randomised groups. In the group receiving the test substance, the swelling had decreased by 50% on the third post-operative day, while in the other two control groups (elevation of the leg, bed rest, with or without the application of ice), no reduction in swelling had occurred at that time. The difference was of major statistical significance. Decreasing pain correlated for the most part with the reduction in swelling. The patients receiving SP became pain-free more rapidly than the control groups. By the 10th day, all patients were free of pain in the SP-treated group. The therapeutic daily dose was 1-2 tablets (5 mg) 3 times daily.

In another double-blind study, the anti-inflammatory enzyme, SP, was evaluated in a group of 70 patients with evidence of cystic breast disease. These patients were randomly divided into a treatment group and a placebo group. SP was noted to be superior to placebo for improvement of breast pain, breast swelling and induration with 85.7% of the patients receiving SP reporting moderate to marked improvement. No adverse reactions were reported with the use of SP. The use of enzymes with fibrinolytic, proteolytic and anti-edemic activities for the treatment of inflammatory conditions of the ear, nose and throat has gained increasing support in recent years.

In a third double-blind study, 193 subjects suffering from acute or chronic ear, nose or throat disorders were evaluated. Treatment with SP lasted 7-8 days, two 5 mg tabs, t.i.d. After 3-4 days treatment, significant symptom regression was observed in the SP-treated group, while this was not noted in the control group. Patients suffering from laryngitis, catarrhal rhinopharyngitis and sinusitis noted markedly rapid improvement. The physicians' assessments of efficacy of treatment were excellent or good for 97.3% of patients treated with SP compared with only 21.9% of those treated with placebo. In a similar study of chronic bronchitis, conducted by a team of otolaryngolosits, the SP-treated group showed excellent results compared with the placebo group in the improvement of loosening sputum, frequency

of cough and expectoration. Other improvements included the posterior nasal hydro rhea and rhinos enosis. The administration of SP reduces the viscosity of the nasal mucus to a level at which maximal transport can be achieved. It has also been demonstrated that the simultaneous use of the peptidase and an antibiotic results in increased concentrations of the antibiotic at the site of the infection.

The mechanisms of action of SP, at the sites of various inflammatory processes consist fundamentally of a reduction of the exudative phenomena and an inhibition of the release of the inflammatory mediators. This peptidase induces fragmentation of fibrinose aggregates and reduces the viscosity of exudates, thus facilitating drainage of these products of the inflammatory response and thereby promoting the tissue repair process. Studies suggest that SP has a modulatory effect on specific acute phase proteins that are involved in the inflammatory process. This is substantiated by a report of significant reductions in C3 and C4 complement, increases in opsonizing protein and reductions in concentrations of haptoglobulin, which is a scavenger protein that inhibits lysosomal protease.

Carpal tunnel syndrome is a form of musculol-igamentous strain caused by repetitive motion injury. Individuals who work at keyboard terminals are particularly susceptible to this condition. While surgery has been considered the first line treatment for carpal tunnel syndrome, recent studies reveal that the use of anti-inflammatory enzymes (e.g. SP and bromelain) in conjunction with vitamins B2 and B6 are also effective. The use of non-invasive, nutritional approaches to the treatment of this common condition will become more important as a generation of keyboard operators approach retirement.

Several research groups have reported the intestinal absorption of SP. SP is well absorbed orally when formulated with an enteric coating. It is known that proteases and peptidases are only absorbed in the intestinal area. These enzymes are mobilized directly to the blood and are not easily detectible in urine. Other enzymes with structural similarities have been reported to be absorbed through the intestinal tract. Chymotrypsin is transported into the blood from the intestinal lumen. Horseradish peroxidase can cross the mucosal barrier of the intestine in a biologically and immunologically active form. Several studies have appeared so far which refer to the systemic effects of orally given proteases and peptidases (e.g. SP), such as repression of oedema and repression of blood vessel permeability induced by histamine or bradykinin. These enzymes also affect the kallikrein-kinin system and the complement system, thus modifying the inflammatory response. In vitro and in vivo studies reveal that SP has a specific, anti-inflammatory effect, superior to that of other proteolytic enzymes.

A review of the scientific literature, including a series of controlled, clinical trials with large patient groups, suggests that Serrapeptase is useful for a broad range of inflammatory conditions. If one considers the fact that anti-inflammatory agents are among the most widely prescribed drugs, the use of a safe, proteolytic enzyme such as SP would be a welcome addition to the physician's armamentarium of physiologic agents.

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The Scientific Basis Behind Alternative Cancer Treatments

by Tanya Harter Pierce, MA, MFCC

This is the second article in a 3-part series on alternative cancer treatments. As mentioned in part 1, a common misconception about alternative approaches to cancer is that they are *not* based on sound medical science. The truth is, however, there are several well-established scientific principles which many alternative cancer treatments are based on, and these have been successfully demonstrated in scientific tests. This article outlines two of the most important principles: the trophoblast principle and the anaerobic cell principle.

The Trophoblast Principle of Cancer

In 1902, Scottish embryologist, Dr. John Beard, observed that cancer cells are virtually indistinguishable from pre-embryonic cells known as "trophoblasts". Within the first 5 days after fertilization, human embryonic cells differentiate into two groups -- embryoblasts, and trophoblasts. Trophoblasts are those cells which go on to form the umbilical cord and placenta. Among the trophoblasts' unique attributes are their ability to grow rapidly and their ability to hide from the mother's immune system. These are the same characteristics that make cancer cells so difficult for the body to defend against.

Dr. Beard discovered that trophoblast cells and cancer cells both hide from their host's immune system by producing a protective protein coating that carries a negative electrostatic charge. White blood cells, a key component of the immune system, being negatively charged themselves, are therefore electrostatically repelled from these cells. This repulsive force inhibits the white blood cells from being able to devour the trophoblast cells of early pregnancy as well as any type of cancer cell in the body.

Even into adulthood, a number of undifferentiated dormant trophoblast-like cells will always be present in every person's body (as detailed in G. Edward Griffin's book *World Without Cancer.*) The purpose of these cells is to provide rapid tissue growth in the event of injury. These trophoblast-like cells are an integral part of the normal healing process. Being undifferentiated, they can create any type of tissue necessary. Under normal conditions, this cellular activity will be turned off when healing is complete. However, when chronic tissue damage exists, such as lung tissue continually exposed to cigarette smoke, the normal control mechanism that turns off trophoblast-like activity can fail. The result may be uncontrolled growth of cancer cells whose original purpose was to repair damaged tissue.

Dr. Beard also discovered that a key organ involved in stopping the uncontrolled growth of trophoblast and cancer cells alike is the pancreas. This is because pancreatic enzymes, as they normally circulate throughout the bloodstream, eat away the negatively charged protective protein coating of these fast-growing cells. Thus, pancreatic enzymes render cancer cells defenseless to the body's immune system. Dr. William Donald Kelly was the first practitioner to put this enzyme theory to the test. He not only cured himself of late-stage cancer using high doses of certain pancreatic enzymes, but also cured thousands of other cancer patients over a number of decades. Enzyme therapy, therefore, reinforces the key natural control mechanism of the body to help it get rid of unwanted cancer cells. Two respected physicians in New York are currently having success focusing on this approach, and many other alternative practitioners are using it as well.

The Anaerobic Cell Principle of Cancer

All cells must be able to meet their energy needs by a process known as cell respiration. There exist many different ways that cells can do this, but these can be separated into two broad categories: those that require oxygen (referred to as "aerobic") and those that do not require oxygen (referred to as "anaerobic".) Under normal, healthy conditions, all of the cells of our body obtain the energy they need by aerobic respiration.

In the 1930s and 1940s, two-time Nobel prize-winning scientist, Otto Warburg, demonstrated that all cancer cells share the important trait of being primarily anaerobic. Whereas all healthy cells in our bodies require an oxygen-rich environment, Warburg was able to show that cancer cells actually thrive in an oxygen-depleted environment. He further proved that, rather than using oxygen, cancer cells use glucose fermentation for their energy needs.

The reason that healthy cells sometimes change from aerobic respiration to anaerobic respiration – and then may turn into cancer cells -- is not entirely understood. However, it is known that under stress, the tissues of the body have a tendency to become more acidic then they would otherwise be. It is also known that oxygen is less able to be assimilated by the body as the cellular environment becomes more acidic. Therefore as the body is stressed by any number of means, such as poor nutrition, toxins, physical stress, or dehydration, the cells of the body may adopt anaerobic respiration as a survival mechanism.

Once in the more primitive anaerobic state, these cells no longer function efficiently and many of the natural mechanisms that control cell division break down, sometimes resulting in cancer.

Based on these scientific facts, some of the most effective alternative cancer therapies exploit the cancer cell's dependency on anaerobic functioning. Cesium high pH therapy and some nutritional/dietary therapies seek to reduce the acidity of the cancer cell and surrounding environment to remove the conditions in which cancer thrives. Another alternative cancer approach, a unique liquid formula called Protocel, inhibits the cancer cell's ability to perform anaerobic respiration, thus causing the cancer cell's energy production to break down and the eventual death of the cancer cell. In the next article of this 3-part series, more details about this remarkable formula will be presented.

As you can see, there are sound scientific principles upon which many alternative cancer therapies are based. And they have proven themselves not only in laboratory tests on mice with cancer, but also in countless human cancer patients. Furthermore, in contrast to radiation, chemotherapy, and surgery, all of the aforementioned alternative therapies exploit the common characteristics of cancer cells, and are able to help the body rid itself of cancer *without* damaging a person's healthy tissues.

The Taxane Limbo: How Low Can We Go?

Clifford Hudis, Chau Dang

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The taxanes are among the most active classes of cytotoxic agents for the treatment of breast cancer and other solid tumors. They have a molecular target (the microtubule), a mechanism of action (enhanced microtubule stability), and reasonably consistent efficacy in metastatic breast cancer ([1]–[3]). After extensive testing in the metastatic setting, we routinely use three drugs, numerous combinations, and several standard dose and schedule alternatives.

Paclitaxel administered intravenously at a dose of 175 mg/m^2 for 3 hours every third week emerged, first, from phase 3 trials in the metastatic setting and was tested as an add-on to standard four-cycle doxorubicin and cyclophosphamide (AC) in the Cancer and Leukemia Group B (CALGB) 9344 and National Surgical Adjuvant Breast and Bowel Project (NSABP) B-28 trials with positive results ([4],[5]). These trials were criticized for failure to use a "best" anthracycline regimen and uneven treatment duration across the arms (ie, four vs eight treatment cycles) ([6]). Subsequent trials that controlled the number of treatment cycles demonstrated that docetaxel given in place of 5-fluorouracil as part of a concurrent combination with AC or in place of several cycles of fluorouracil, epirubicin, and cyclophosphamide (FEC) was superior; since then, a number of trials have been reported with mostly positive results regardless of anthracycline comparator, taxane choice, dose, or schedule ([7],[8]). A recent meta-analysis of the published studies reported relatively constant risk reductions for both recurrence and death across the two tested taxanes ([9]).

Despite these seemingly consistent data, controversy continues. With the goal of maximizing benefit, we ask is there a best taxane and/or a best schedule? And with a goal of limiting toxicity, we ask how can we limit treatment (dose size and cycle number) and/or who can we not treat?

A best taxane might be defined through consideration of activity, toxicity, and expense, but these many variables complicate interpretation of the available head-to-head trials of the three agents in the metastatic setting, which have not established a consistent and overall drug-specific advantage that is independent of dose and schedule ([10]).

The optimal dose and schedule is probably agent specific. Weekly paclitaxel appears to be consistently more active and differently toxic ([11]–[13]). For docetaxel, weekly

administration does not offer the same advantage, and it is worth noting that some patients and clinicians would probably prefer less frequent therapy, all else being equal (14). For albumin-bound paclitaxel, phase 3 comparative data are not yet available on this issue (15,16).

Patient selection for adjuvant chemotherapy is a key goal of current research programs. In the metastatic setting, there are (or perhaps must be) some tumors that are simply not sensitive to chemotherapy or not sensitive to taxane therapy or that possess differential sensitivity to these agents. Notably, there are no established predictive factors used in the metastatic setting to select for or against the routine use of taxanes and no consistent preclinical data in this regard (17–19). Further, neither hormone receptor status nor HER2 expression has consistently predicted the benefits of taxanes in the metastatic setting. The adjuvant setting adds a layer of complexity because it includes some or many postoperative patients who are not destined to experience recurrence before death from other causes. Judging the benefits of specific drugs against specific tumors (ie, assessing a predictive factor) is impossible if there is no tumor to assess. In such a situation, so-called predictive factors incorporate both drug–tumor interactions and tumor–host interactions to be useful.

The burning question then is whether hormone receptor status and HER2 expression can serve as predictive factors for the use of taxanes. An unplanned retrospective analysis of the CALGB 9344 trial that was based on estrogen receptor (ER) status indicated that the benefit of adding paclitaxel was substantially greater in patients with ER-negative tumors than in patients with ER-positive tumors (4). A benefit for patients with ER-positive tumors was not, however, excluded. A subsequent analysis (20) of several CALGB trials demonstrated a consistent effect: so-called better chemotherapy was most clearly superior in patients with ER-negative tumors and the impact among those with ER-positive breast cancer was about half as large. From a practical point of view, there were potential limits on the clinical application of this result because there was no untreated control group (meaning the series does not address the "any vs none" question) and ER testing was not centrally performed or reviewed.

Recent developments challenge this CALGB hypothesis. In the subset of patients with HER2-positive breast cancer, there was some evidence that the use of targeted agents (eg, trastuzumab) levels this playing field so that, in terms of efficacy, specific chemotherapy agent choice is less critical (11,21–24). However, a recent reanalysis of data from the CALGB 9344 trial (25) demonstrated that HER2 status predicted the benefit of adding paclitaxel regardless of ER status. This latter point bears emphasis because it plainly highlights the fact that ER status in isolation cannot serve as a decision point for the use of taxanes (or any specific chemotherapy agent or regimen). In addition, other groups of investigators have not consistently identified ER status as a predictor of taxane benefits in general or with regard to schedule (9, 26).

The study by Martín et al. (27) in this issue of the Journal is an important addition to the ongoing discussion of the role of the taxanes in the adjuvant setting. This trial of the Grupo Español para la Investigación del Cáncer de Mama (Spanish Group for the

Investigation of Breast Cancer), GEICAM 9906, compares a better anthracycline-containing regimen (six cycles of FEC using epirubicin at a dose of 90 mg/m^2) against a sequence of the same version of FEC for four cycles followed by eight doses of weekly paclitaxel. This trial directly addresses the concerns of earlier critics that an inferior and shorter anthracycline regimen loaded the dice in favor of the taxane arms. Moreover, the paclitaxel dose and schedule do appear to be the best ones as well, as demonstrated by recently reported randomized studies in both the metastatic and adjuvant settings ([11],[12],[26]). Martín et al. ([27]) report an overall benefit that was very consistent with the results of earlier trials. However, when they used centralized testing on a large subset (74%) of the patients, they failed to confirm the results of the earlier ER- and HER2-driven retrospective subset analyses. Simply stated, Martín et al. ([27]) show a benefit for 8 weeks of paclitaxel, which replaces two cycles of FEC, regardless of ER or HER2 status. This result is generally consistent with those of the Breast Cancer International Research Group 001 ([7]), Programmes d'Actions Concertées Sein 01 ([8]), and Eastern Cooperative Oncology Group E-1199 ([26]) trials.

For fans of biologically based subset analyses who believe that they can provide information for clinical practice that are based on exploratory studies, these data are a problem. If earlier reports led you to conclude that ER and HER2 status predict the benefits of adding taxanes, how do you explain the results of the GEICAM 9906 trial and other studies? Is weekly paclitaxel so much better than every third week treatment that it compensates for the latter's inferior efficacy with ER-positive, HER2-negative disease? This conclusion seems unlikely given the inconsistent associations across taxanes, doses, and schedules. Was their study underpowered to exclude a difference by hormone receptor and HER2 status? This conclusion is possible, but, if we saw only their present data, we would not be tempted to pursue this question. Could laboratory testing variability explain the seemingly inconsistent results? This question is harder to address, but, notwithstanding the well-documented issues of laboratory testing variability, most laboratories get most hormone receptor and HER2 test results right. Is FEC somehow different from AC with regard to an impact on subsequent taxane benefit in ER and HER2 subsets? The recent E-1199 results suggest that it is not; however, upcoming results from the NSABP B-30 trial may allow us to address this issue ([26]). Finally, could hormone receptor–positive breast cancer really be a collection of more or less sensitive subtypes (ie, luminal A vs B) with less or more chemotherapy senstitivity, respectively? If individual trials varied in their randomization of these subsets, we might see the present mixture of positive and negative associations.

From a practical point of view, Martín et al. ([27]) underscore the clinically significant risks physicians face when using unplanned subset analyses to guide clinical practice. We need to be reminded from time to time that hypothesis-generating subset analyses are just that—hypothesis generating—and not practice changing unless and until they are confirmed prospectively ([28]). In this case, the retrospectively generated hypothesis was that hormone receptor and HER2 status would predict the value of adding paclitaxel with sufficient accuracy as to allow clinicians to select patients for this chemotherapy agent. The prospective study by Martín et al. ([27]) join a rapidly growing list of studies that do not support that hypothesis ([9],[26],[27]). If you accept that the taxanes are effective,

hormone receptor and HER2 status should not routinely guide your selection of patients for this therapy.

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