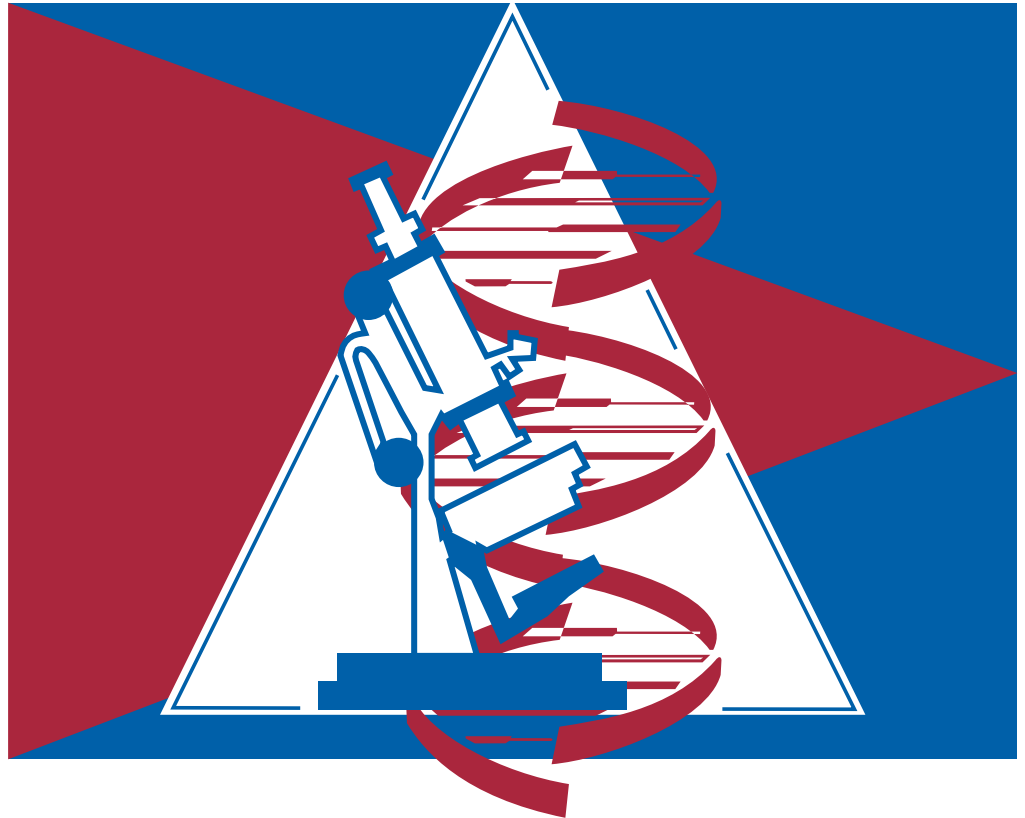


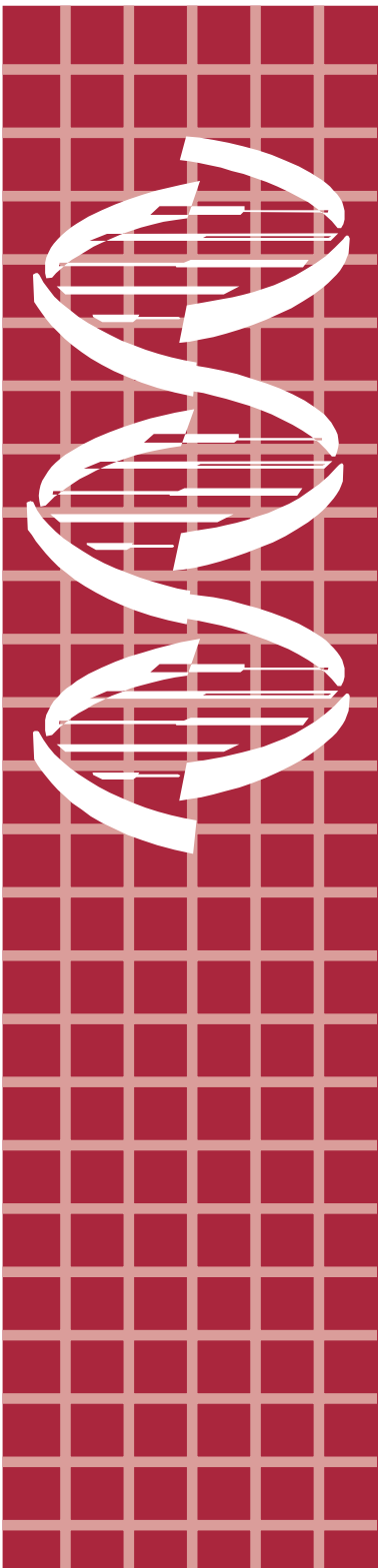
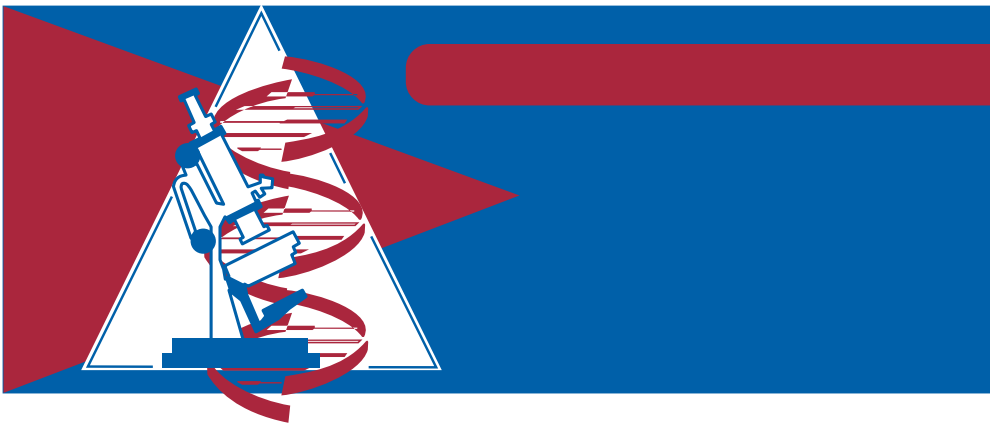
Diagnostic Cytology, Histology and Molecular Pathology

OncoDiagnostic Laboratory, Inc.



FYI Breast Cancer

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WHAT IS BREAST CANCER?

Breast cancer is cancer that affects the breast. The vast majority of breast cancer occurs in women, although men can develop breast cancer too.

Cancer is the name for a group of diseases in which the body's cells are changed in appearance and function. Such abnormal cells can grow out of control and form a mass or "*tumor*." When abnormal cells originate in the breast tissue, the mass is called a *breast tumor*.

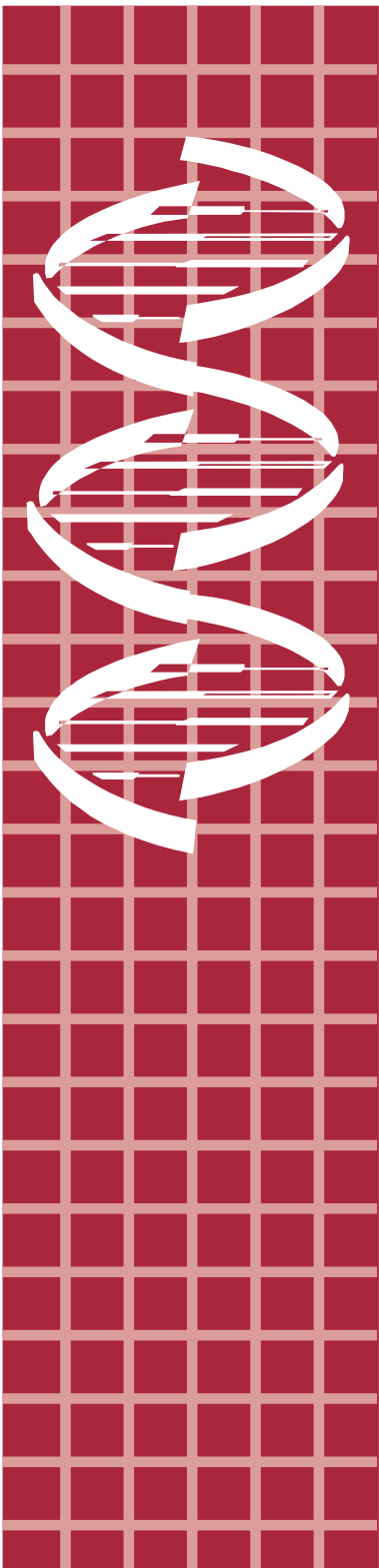
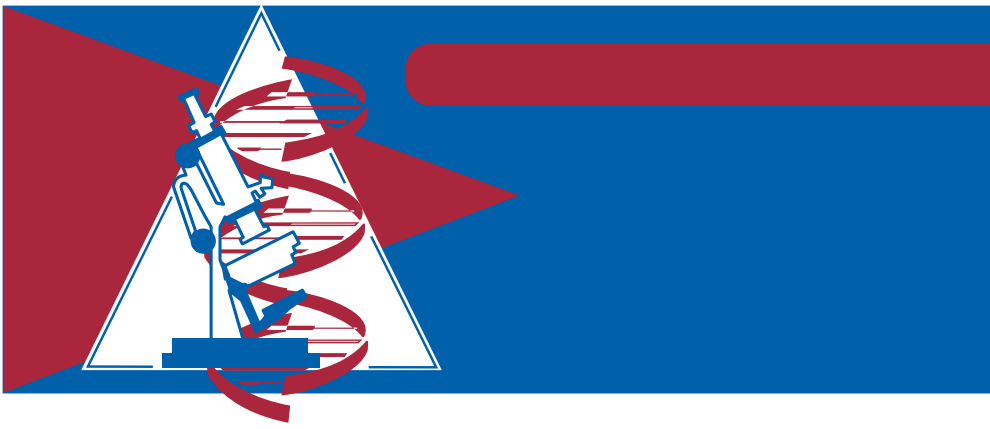
A breast tumor is considered *benign* if it is limited to a few cell layers and does not invade surrounding tissues or organs. Yet if the tumor spreads to surrounding tissues or organs, it is considered *malignant*, or *cancerous*. *Carcinoma* is the term used to describe most common cancers that arise from epithelial (surface or lining) tissues. By contrast *sarcoma* is the term used to define tumors that arise from bone, muscle, fat or connective tissue.

The breasts are in essence, a collection of fatty tissue and glands that have been adapted to secrete milk after a woman gives birth. The glands that produce milk are called lobules and the tubes that connect them to the nipples are called ducts. Correspondingly, carcinoma of the breast develops when malignant changes occur in the cells that line the lobules or, more commonly, the ducts.

There are two major types of breast cancer: *lobular carcinoma* and *ductal carcinoma*. These are generally known as "*in situ*" carcinomas – they are confined to the original site. The majority of breast cancers (70% - 80%) arise from the ducts, which make up the bulk of breast tissue. Since lobular and ductal cells are found in the glandular tissues of the upper, central, and outer regions of the breast, this is where most breast cancers occur. Breast tumors rarely arise in the fatty or nonglandular tissue. Such tumors, when they appear, are usually sarcomas.

WHAT ARE THE INCIDENCES OF BREAST CANCERS?

Breast cancer is the most common cancer among women, excluding nonmelanoma skin cancers. The American Cancer Society estimates that in 2001 about 192,200 new cases of invasive breast cancer (Stages I-IV) will be diagnosed among women in the United States. Ductal carcinoma in situ (DCIS) accounts for about 39,900 new cases each year. DCIS (stage 0) is noninvasive and is the earliest form of breast cancer. Breast cancer also occurs in men. An estimated 1,500 cases will be diagnosed among men.



WHAT ARE THE RISK FACTORS FOR BREAST CANCER?

Factors that cannot be changed

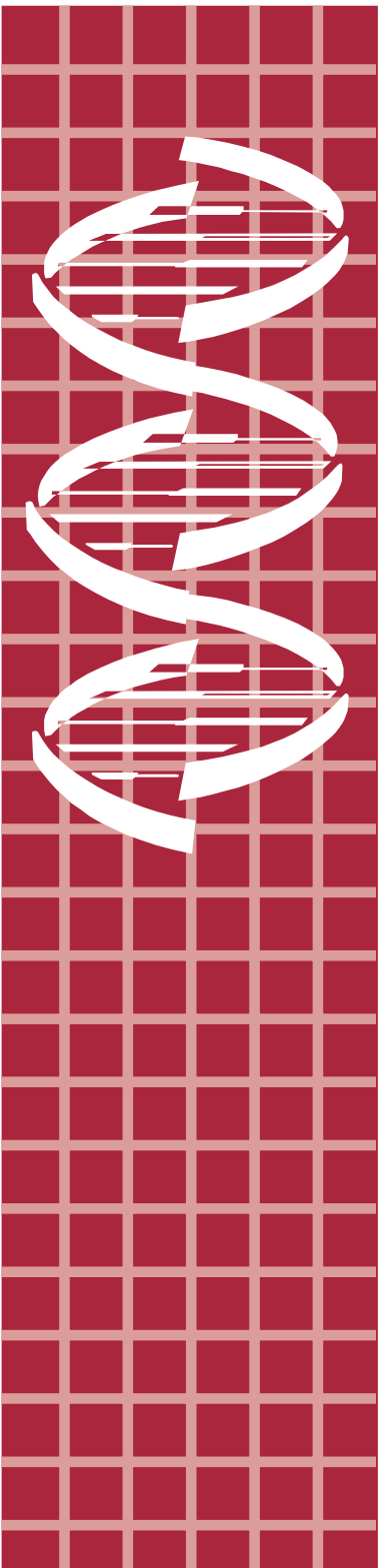
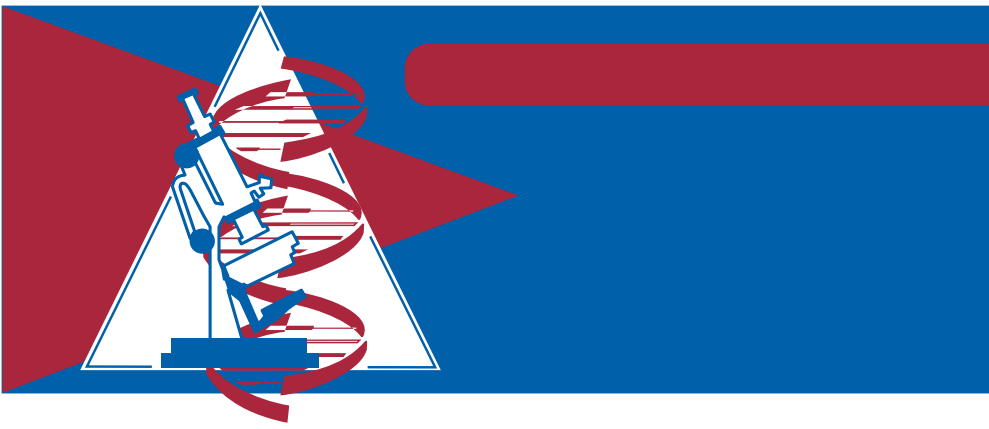
Gender: Simply being a woman is the main risk factor for developing breast cancer. Breast cancer can affect men, but this disease is about 100 times more common among women than men.

Aging: A woman's risk of developing breast cancer increases with age. About 77% of women with breast cancer are over age 50 at the time of diagnosis. Women younger than 30 years account for only 0.3 % of breast cancer cases.

Genetic Factors: Recent studies have shown that about 10% of breast cancer cases are directly due to inherited mutations (changes) in breast cancer related genes and that most of these results are from mutations of the BRCA1 and BRCA2 genes. Normally, these genes help to prevent cancer by making proteins that keep cells from growing abnormally. However, if a person has inherited a mutated gene from either parent, chances of developing breast cancer increase. About 50% to 60% of women with inherited BRCA1 or BRCA2 mutations will develop breast cancer by the age of 70. Women with these inherited mutations also have an increased risk for developing ovarian cancer.

Inherited mutations of the p53 tumor suppressor gene can also increase a woman's risk of developing breast cancer, as well as leukemia, brain tumors, and/or carcinomas (cancer of bones or connective tissue). However, this inherited gene mutation, known as Li-Fraumeni syndrome (named after the founders), is a rare cause of breast cancer.

Family History: Breast cancer risk is higher among women whose close blood relatives have this disease. Blood relative can be from either the mother's or father's side of the family. Having one first-degree relative (mother, sister, or daughter) with breast cancer approximately doubles a woman's risk, and having two first-degree relatives increases their risk 5-fold. Although the exact risk depends on several factors, women with a family history of breast cancer in male family members also have an increased risk of breast cancer.



Personal history: 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 of the first cancer.

Race: White women are slightly more likely to develop breast cancer than are African-American women. But African Americans are more likely to die of this cancer because they are often diagnosed at an advanced stage when breast cancer is harder to treat and cure. Asian, Hispanic, and American Indian women have a lower risk of developing breast cancer.

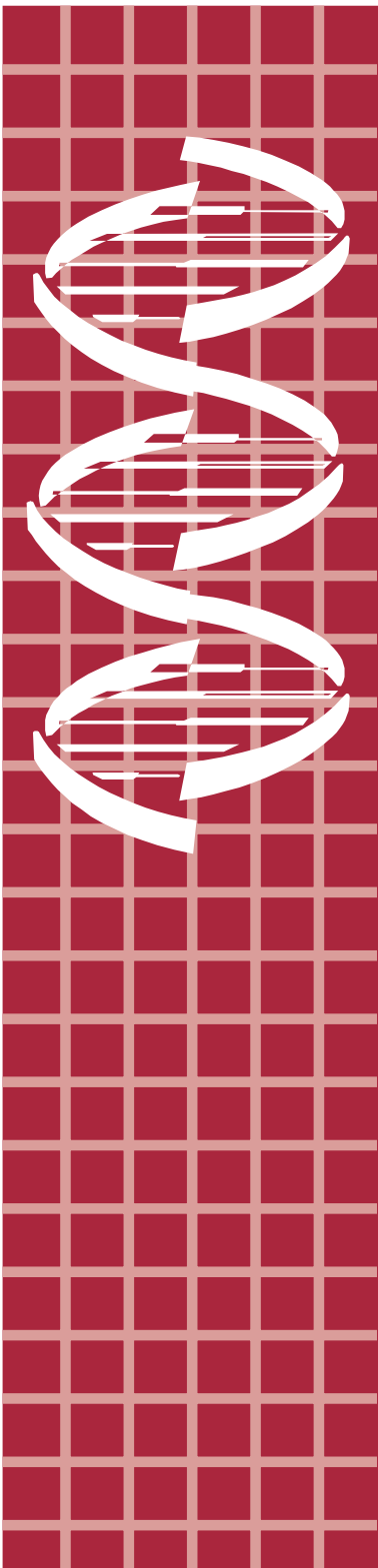
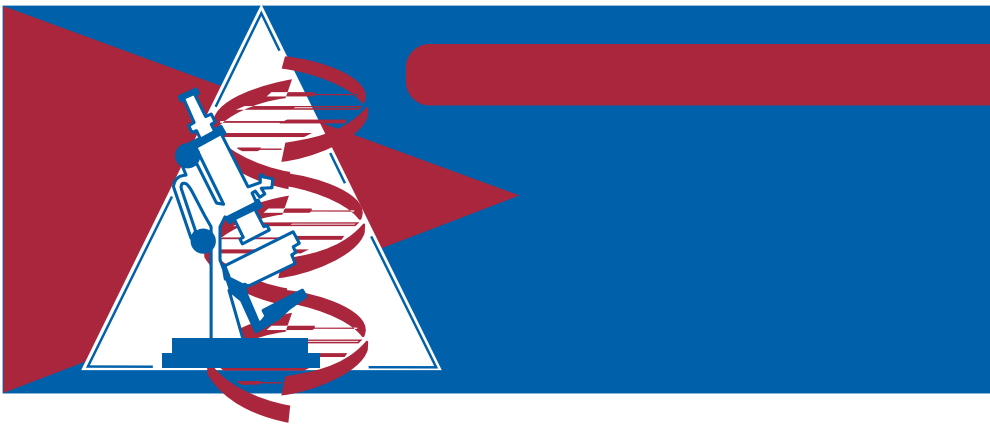
Previous breast biopsy: Women whose earlier breast biopsies were diagnosed as “proliferative breast disease without atypia” (usual hyperplasia) have a slightly higher risk of breast cancer (1.5 to 2 times greater than other women do). A previous biopsy result of atypical hyperplasia increases a woman’s breast cancer risk by 4 to 5 times. Having a biopsy diagnosed as fibrocystic changes without proliferative breast disease does not affect breast cancer risk.

Previous breast irradiation: Women who have had chest area radiation therapy as a child or young woman, as treatment for another cancer (such as Hodgkin’s disease or non-Hodgkin’s lymphoma) are at significantly increased risk for breast cancer.

Menstrual periods: Women who started menstruating at an early age (before age 12) or who went through menopause at a late age (after age 50) have a slightly higher risk of breast cancer.

Factors related to lifestyle

Oral contraceptive use: It is still not clear what part oral contraceptives (birth control pills) might play in breast cancer risk. A recent analysis using data from most of the large, well-designed, published studies found that women now using oral contraceptives have a slightly greater risk of breast cancer than those women not using them. Women who stopped using oral contraceptives more than 10 years ago do not appear to have any increased breast cancer risk. When considering using oral contraceptives, women should discuss their other risk factors for breast cancer with their health care team.



Not having children: Women who have had no children or who had their first child after age 30 have a slightly higher breast cancer risk.

Hormone replacement therapy: Most studies suggest that long-term use (5 years or more) of hormone replacement therapy (HRT) after menopause may slightly increase the risk of breast cancer.

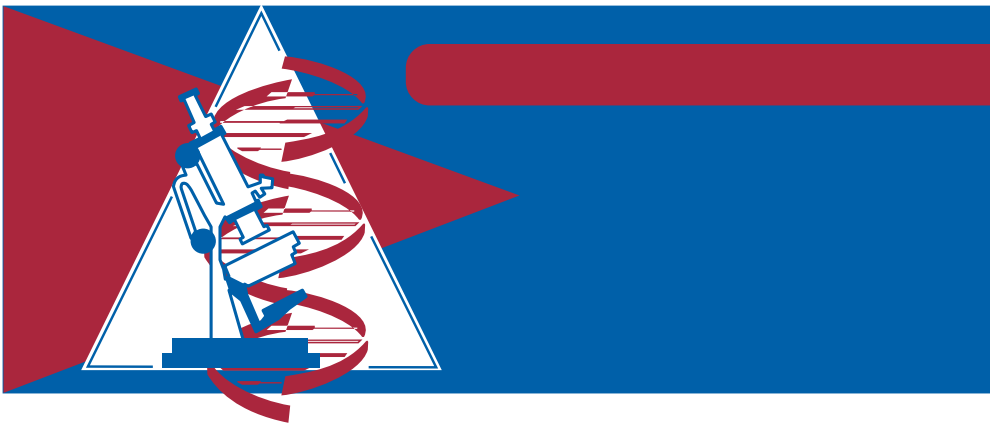
The decision to use hormone replacement therapy after menopause should be made by a woman and her doctor after weighing the possible risks and benefits. Factors to consider include her other risk factors for heart disease, breast cancer, osteoporosis (thinning and weakening of bones), and the severity of menopausal symptoms.

Not breast feeding: Some studies suggest that breast feeding may slightly lower breast cancer risk, especially if breast feeding is continued for 1.5 to 2 years. Other studies found no impact on breast cancer risk.

Alcohol: Use of alcohol is clearly linked to increased risk of developing breast cancer. Compared with nondrinkers, women who consume one alcoholic drink a day have a very small increase in risk, and those who have 2 to 5 drinks daily, have about 1.5 times the risk of women who drink no alcohol. Alcohol is also known to increase the risk of developing cancers of the mouth, throat, and esophagus. The American Cancer Society recommends limiting your consumption of alcohol, if you drink at all.

Obesity and high fat diet: Obesity (being overweight) is associated with an increased risk of developing breast cancer, especially for women after menopause (which usually occurs at age 50). Although most of a woman's estrogen is produced by her ovaries, fat tissue can change some other hormones into estrogen. Having more fat tissue can increase a woman's estrogen levels, and increase her likelihood of developing breast cancer.

Physical inactivity: Exercise and cancer is a relatively new area of research. Recent studies indicate that strenuous exercise in youth might provide life-long protection against breast cancer, and that even moderate physical activity as an adult can lower breast cancer risk. Additional research is underway to confirm these findings.



Environmental pollution: A great deal of research has been reported and more is under way in the field of environmental influences on breast cancer risk. The goal is to determine their possible relationships to breast cancer.

CAN BREAST CANCER BE PREVENTED?

Preventive mastectomy is a surgical procedure chosen occasionally by a woman who is at very high risk for breast cancer. The purpose is to reduce risk by removing both breasts before breast cancer is diagnosed. The reasons for considering this type of surgery may include one or more of the following risk factors: mutated BRCA genes found by genetic testing, previous cancer in one breast, strong family history (breast cancer in several close relatives), and/or biopsies showing lobular carcinoma in situ (LCIS).

There is no certain way to prevent breast cancer. For now, the best plan for women at average breast cancer risk is to reduce risk factors whenever possible as noted in “What are the Risk Factors For Breast Cancer?” Following the guidelines for early detection as outlined in “Can Breast Cancer be Found Early?” will not prevent breast cancer, but can help find cancers when the likelihood of successful treatment is greatest.

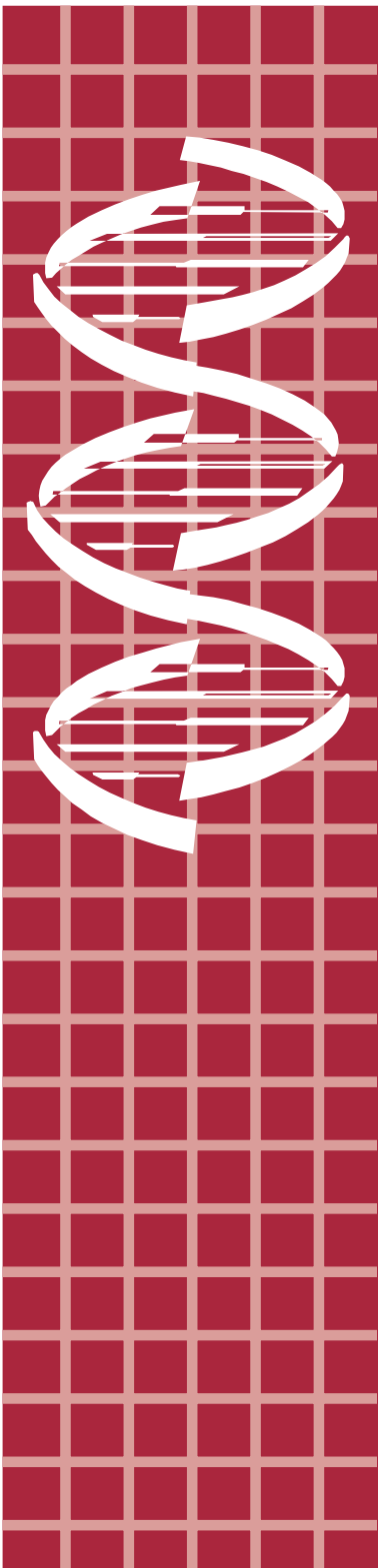
DO WE KNOW WHAT CAUSES BREAST CANCER?

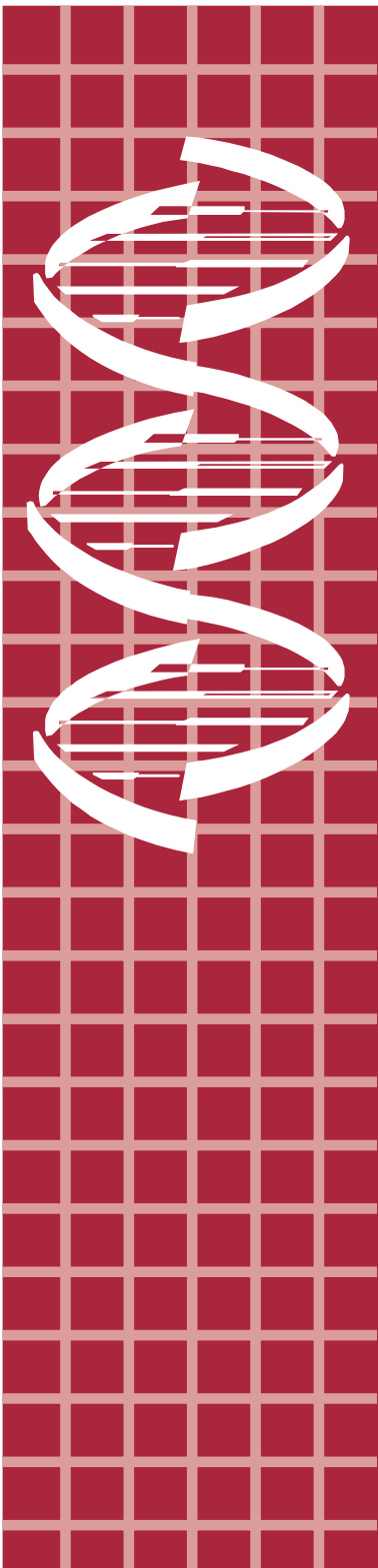
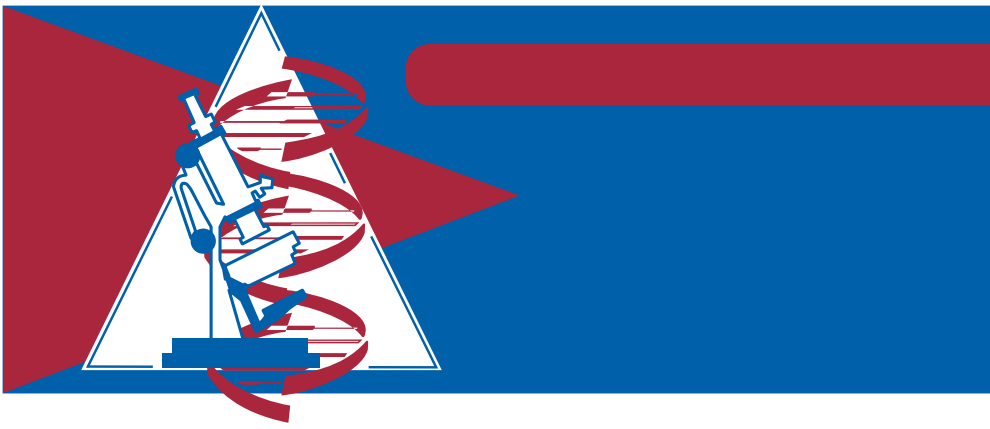
Although we know some of the risk factors that increase a woman’s chance of developing breast cancer, we do not yet know what causes most breast cancers or exactly how some of these risk factors cause cells to become cancerous. Research is under way to learn more.

CAN BREAST CANCER BE FOUND EARLY?

Following these guidelines for the early detection of breast cancer improves the chances that breast cancer can be diagnosed at an early stage and treated successfully.

Women aged 20 or older should have a clinical breast examination by a health professional every 3 years and perform breast self-examination (BSE) every month. By doing the self exam regularly, you get to know how your breasts normally feel and you can more readily detect any change. If a change occurs, such as development of a lump or swelling in the breast or underarm area, skin irritation or dimpling, nipple pain or retraction (turning inward), redness or scaliness of the nipple or breast skin, or



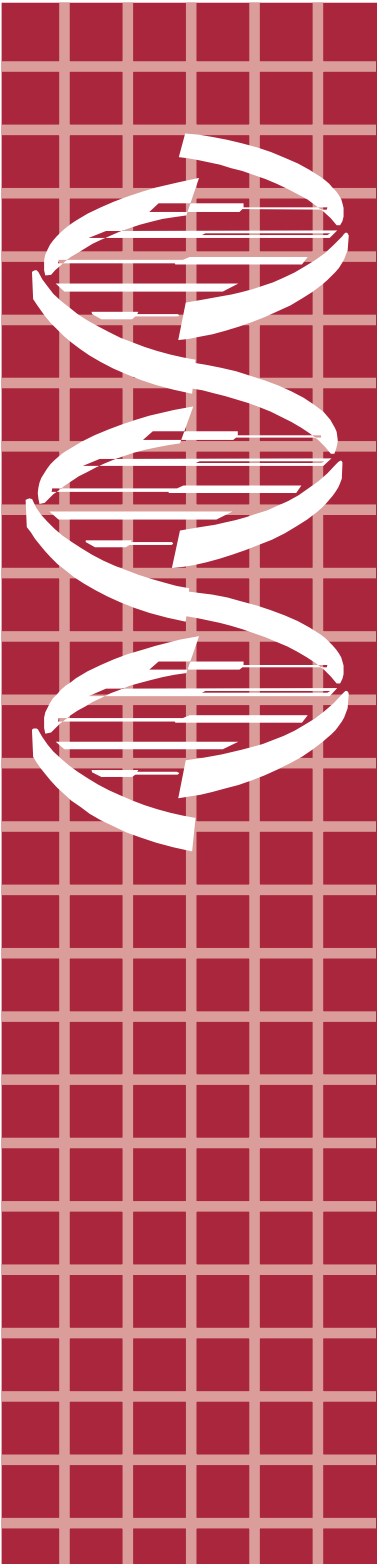
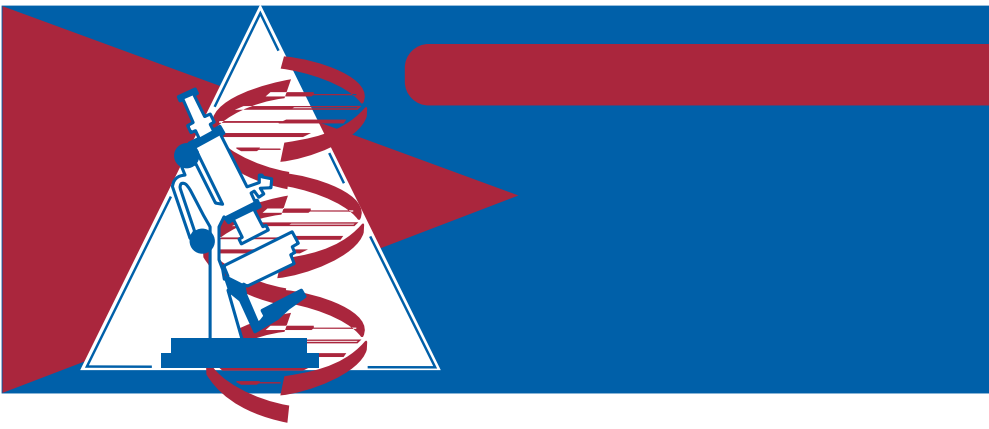


a discharge other than breast milk, you should see your health care provider as soon as possible for evaluation. However, remember that most of the time, these breast changes are not cancer.

Clinical breast examination: A clinical breast examination (CBE) is an examination of your breasts by a health professional, such as a physician, nurse practitioner, nurse, or physician assistant. For this examination, you undress from the waist up. The health professional will first inspect (look at) your breast for changes in size or shape. Then, using the pads of the fingers, the examiner will gently palpate (feel) 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. During the CBE is a good time for the health professional to teach breast self-examination to the woman who does not already know how to examine her breasts. Ask your doctor or nurse to teach you and watch your technique.

Breast self-examination: The best time for breast self examination (BSE) is about a week after your period ends, when your breasts are not tender or swollen. If you are not giving regular periods, do BSE on the same day every month.

- Lie down with a pillow under your right shoulder and place your right arm behind your head.
- Use the finger pads of the three middle fingers on your left hand to feel for lumps in the right breast.
- Press firmly enough to know how your breast feels. A firm ridge in the lower curve of each breast is normal. If you're not sure how hard to press, talk with your doctor or nurse.
- Move around the breast in a circular, up and down line, or wedge pattern. Be sure to do it the same way every time, check the entire breast area, and remember how your breast feels from month to month.
- Repeat the exam on your left breast, using the finger pads of the right hand. (Move the pillow to under your left shoulder.)



- If you find any changes, see your doctor right away.
- Repeat the examination of both breasts while standing, with your one arm behind your head. The upright position makes it easier to check the upper and outer part of the breasts (toward your armpit). This is where about half of breast cancers are found. You may want to do the standing part of the BSE while you are in the shower. Some breast changes can be felt more easily when your skin is wet and soapy.

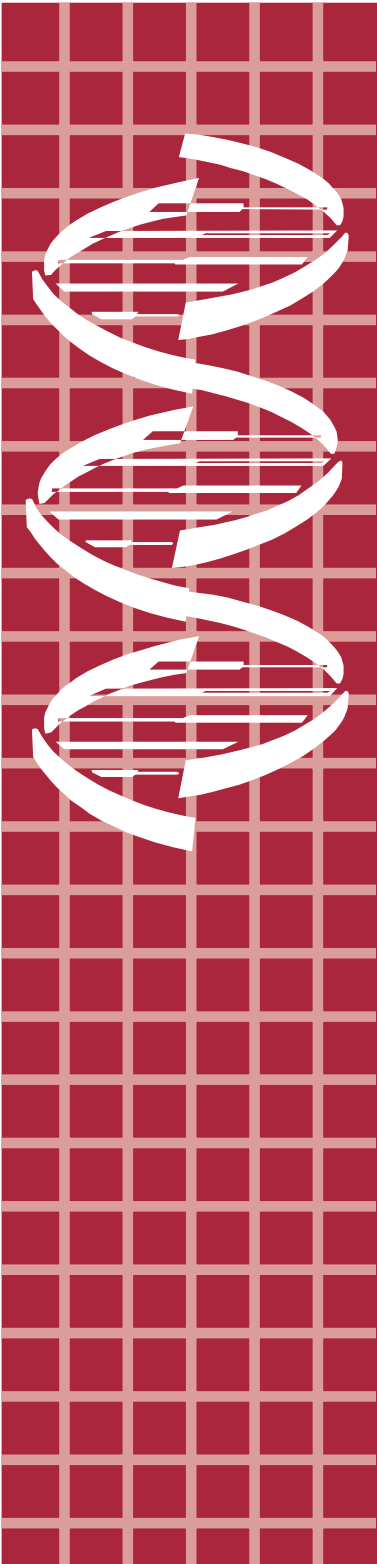
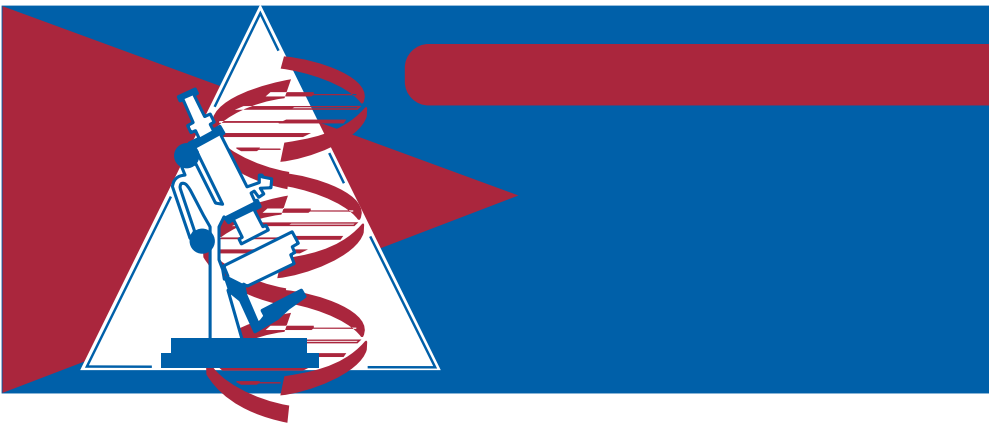
For added safety, you can check your breasts for any dimpling of the skin, changes in the nipple, redness, or swelling while standing in front of a mirror right after your BSE each month.

Women aged 40 and older should have a screening mammogram and a breast exam by a health professional every year.

Mammography: A mammogram is a x-ray of the breast. *Diagnostic mammography* is used to diagnose breast disease. *Screening mammography* is used to look for breast disease in women who are asymptomatic, that is, they appear to have no breast problems.

Although breast x-rays have been performed for more than 70 years, modern mammography has only existed since 1969. That was the first year x-ray units dedicated to breast imaging were available. With modern mammography equipment used specifically for breast x-rays, very low levels of radiation are used, usually about 0.1 to 0.2 rad dose per x-ray. Strict guidelines are in place to assure that mammography equipment is safe and uses the lowest dose of radiation possible. Many people are concerned about the exposure to x-rays, and rightly so, but the level of radiation in up-to-day mammograms does not significantly increase the risk for breast cancer. To put dose into perspective, a woman who receives radiation as a treatment for breast cancer will receive several thousands rads. If a woman had yearly mammograms beginning at age 40 years and continuing until 90, she will have received 10 rads. As another example, one mammogram exposes a woman to roughly the same amount of radiation as flying from New York to California on a commercial jet.

In order to perform a mammogram, the breast is compressed to flatten and spread the tissue. Although this may be temporarily uncomfortable, it is



necessary in order to produce a good mammogram. The compression only lasts a few seconds, and the entire procedure for screening mammography takes about 20 minutes. This procedure produces a black and white image of the breast tissue on a large sheet of film that is “read,” or interpreted, by a radiologist. The physician reading the films will look for several types of changes.

Calcifications, or microcalcifications, are tiny mineral deposits within the breast tissue which appear as small white spots on the film. They may occur singly or in clusters. They are a sign of changes within the breast that can either be monitored by additional, periodic mammograms, or can be examined by biopsy (removal of a small amount of breast tissue). They may be caused by benign breast conditions, or, less often, by breast cancer. Another important change that can be seen on a mammogram is a mass, which may occur with or without calcifications. Masses can be due to many things, including cysts and fibroadenomas, but may be cancer and usually should be biopsied if they are not fluid-filled cysts.

A *cyst*, which is a benign collection of fluid in the breast, cannot be diagnosed by physical exam alone, nor can it be diagnosed by mammography alone. Either breast ultrasound, or removal of the fluid with a needle (aspiration), is used to confirm that a mass is a cyst. If a mass is not a cyst, then further imaging may be obtained.

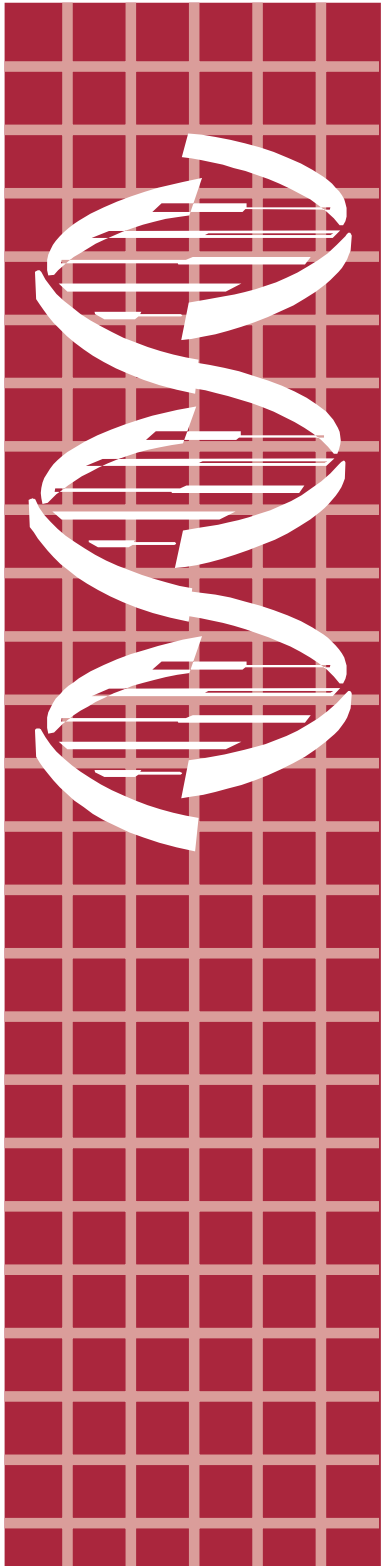
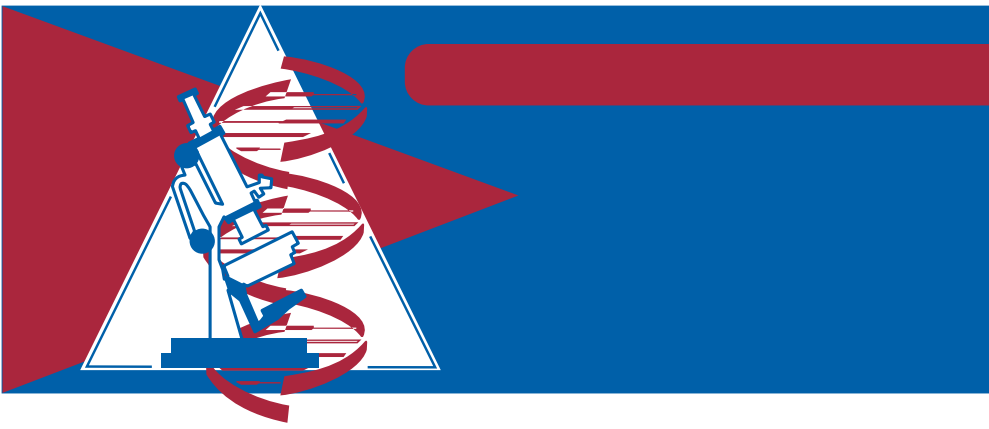
As with calcifications, a mass can be caused by benign breast conditions, or by breast cancer. Some masses can be monitored with periodic mammograms, while others may require immediate or delayed biopsy.

A mammogram, while suggestive, cannot prove that an abnormal area is cancer. To confirm whether cancer is present, a small amount of tissue must be removed and examined under a microscope. This procedure is called a biopsy.

HOW IS BREAST CANCER DIAGNOSED?

It is important to remember that a lump or other changes in the breast, or an abnormal area on a mammogram, may be caused by cancer or by other, less serious problems.

To determine the cause of any signs or symptoms, your physician will perform a careful physical exam that includes:



- Personal and family medical history
- Current overall health status
- One or more of these breast exams:
 - **Palpation:** Carefully feeling the lump and the tissue around it, its size, its texture and whether it moves easily. Benign lumps often feel different from cancerous ones.
 - **Diagnostic mammography:** X-ray procedure of the breast.
 - **Ultrasonography:** High-frequency sound waves, not heard by humans. The sound waves enter the breast and bounce back. The pattern of their echoes produce a picture called a sonogram, which is displayed on a screen. The exam is often used along with mammography.

Based on these exams, your physician may decide that no further test are needed and no treatment is necessary. In such cases, your physician may want to check you regularly to watch for any changes.

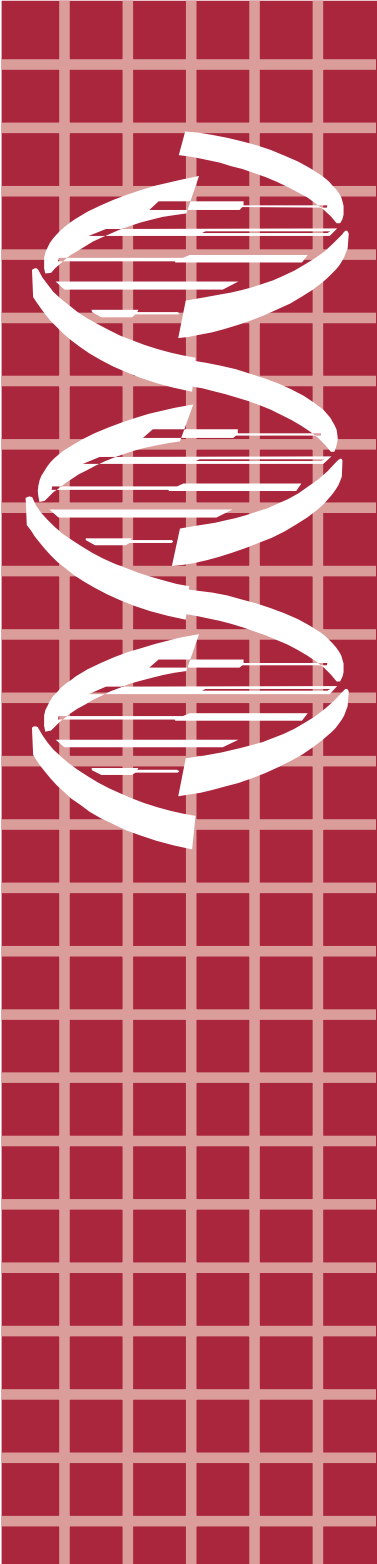
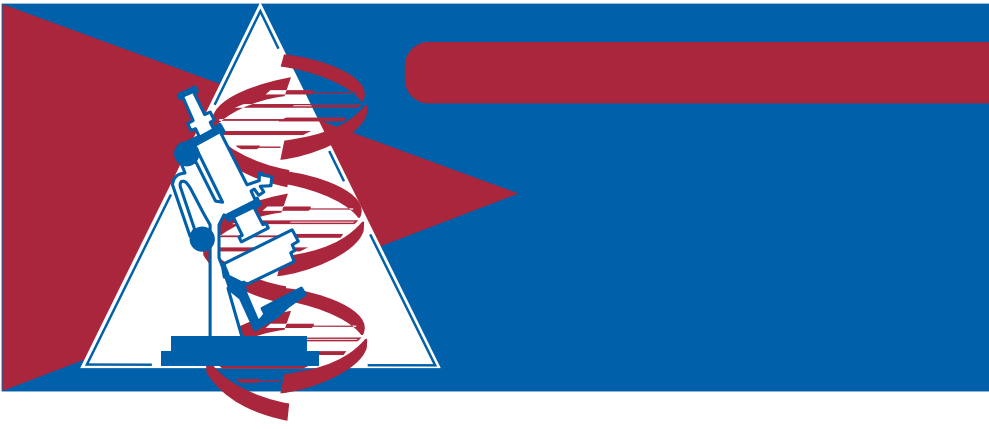
Often, however, the physician must remove fluid or tissue from the breast to be sent to a laboratory for diagnosis. This procedure is called a biopsy, and there are several types:

- **Image-guided biopsies**
Those aided by ultrasound or other imaging technique
- **Needle aspiration**
A very fine needle is guided into the suspicious area and fluid from a cyst or cells from a tumor are removed for examination under the microscope.
- **Core needle biopsy**
A larger needle is guided into the lump to remove a small cylinder of tissue.
- **Surgical biopsy**
A surgeon removes part or all of a lump or suspicious area,

All of the above biopsies are then followed by a pathological examination of the tissue or fluid to check for cancer cells.

LABORATORY TESTING OF BREAST CANCER BIOPSY SAMPLES

The tissue removed during a biopsy is examined in a laboratory to see whether the cancer is *in situ* (not invasive) or invasive. The biopsy is also used to determine the cancer's type and grade. The grade helps predict the patient's prognosis because cancers that closely resemble normal breast tissue tend to grow and spread more



slowly. In general, a lower grade number indicates a slower-growing cancer while a higher number indicates a faster-growing cancer.

The following are the most common laboratory tests done on breast tissue that is diagnosed with cancer:

Estrogen and progesterone receptors (hormone receptor status):

Hormone receptor status testing is recommended as part of an initial workup of invasive breast cancer. It is not diagnostic but helps the doctor to determine treatment options and to understand more about the tumor's characteristics.

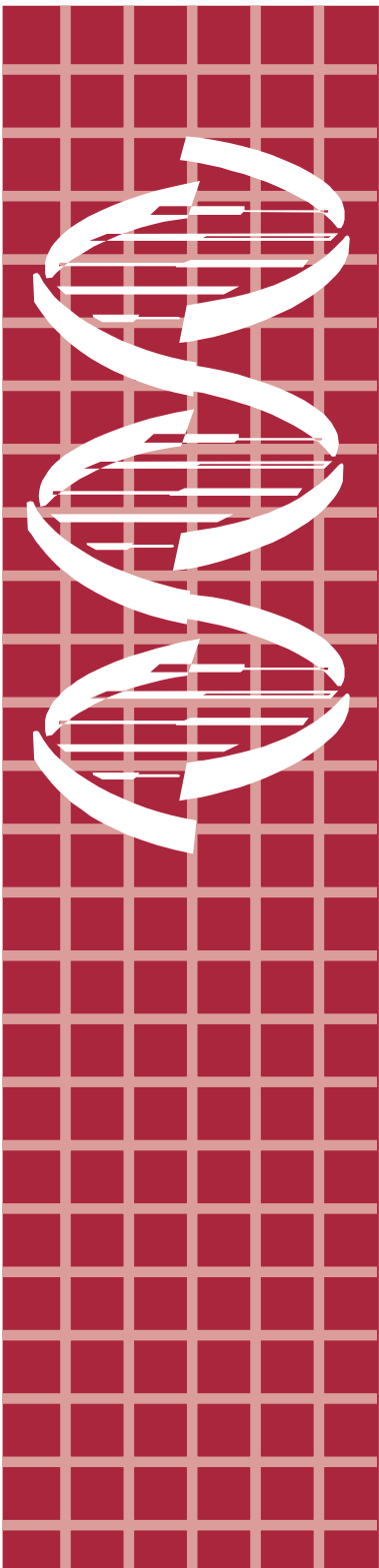
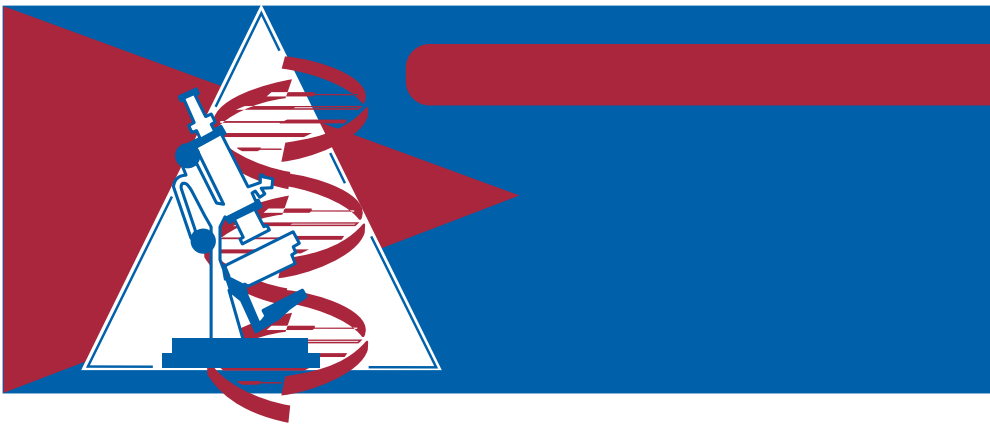
In general, if a patient's cancer is ER- and PR-positive, the patient will have a better-than-average prognosis, and their cancer is likely to respond to endocrine therapy (anti-hormone treatments). The more receptors present and the more intense their reaction, the more likely the response. However, an individual's response depends on a variety of factors.

If a patient's cancer is ER-negative but PR-positive, the patient may still benefit from endocrine therapy but may have a diminished response. If the cancer is both ER- and PR-negative, then the patient will probably not benefit from endocrine therapy.

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, the cells are said to be diploid. If the amount is abnormal, then the cells are described as aneuploid. Some studies have found that aneuploid breast cancers tend to be faster growing and more likely to come back. *Flow cytometry* and *Image cytometry* are the 2 common tests used to determine whether breast cancer cells are diploid or aneuploid.

In addition, Flow cytometry can also measure the S-phase fraction, which 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, which identifies cells in the S-phase, as well as cells getting ready to replicate DNA, cells that have just completed DNA replication, and cells in the process of dividing.



HER2/neu testing: HER2/neu testing is done on thin slices of the biopsy sample that are treated with special antibodies that identify the HER2/neu protein or with pieces of DNA that identify the HER2/neu gene.

About 1/3 of breast cancers have too much of a growth-promoting protein called HER2/neu and too many copies of the gene that instructs the cells to produce that protein. In other cases, a normal number of HER2/neu genes are present, but they are too active in instructing the cells to produce HER2/new protein.

These cancers tend to grow and spread more aggressively than other breast cancers. They can be treated with a drug called Herceptin that prevent the HER2/new protein from stimulating breast cancer cell growth.

CAN BREAST CANCER BE TREATED?

Yes. Prompt treatment is essential. Without surgery, radiation, or chemotherapy, a woman who has breast cancer will almost surely die. Fortunately, the chances for long-term survival – and cure – are excellent if the cancer is caught early enough.

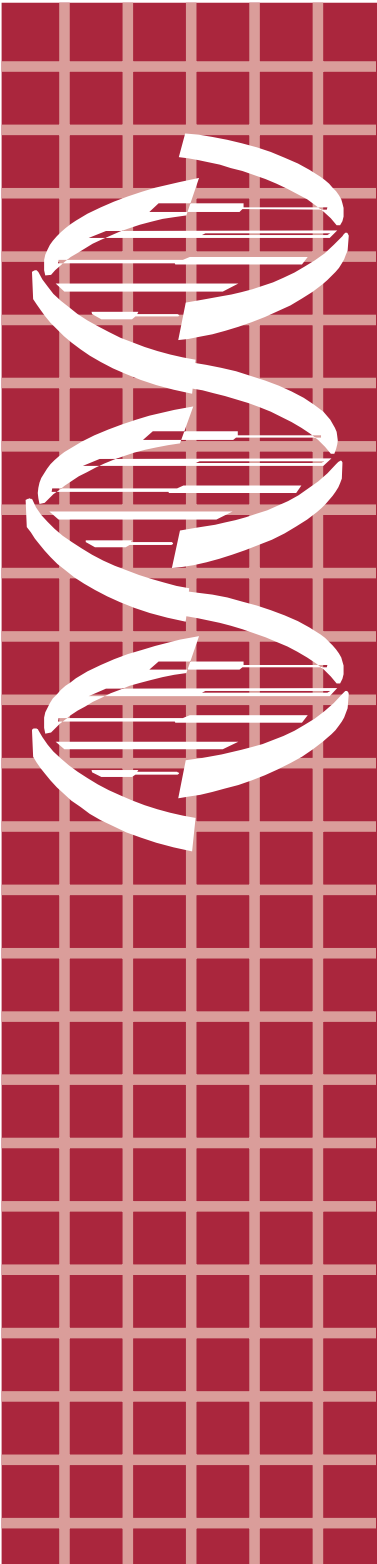
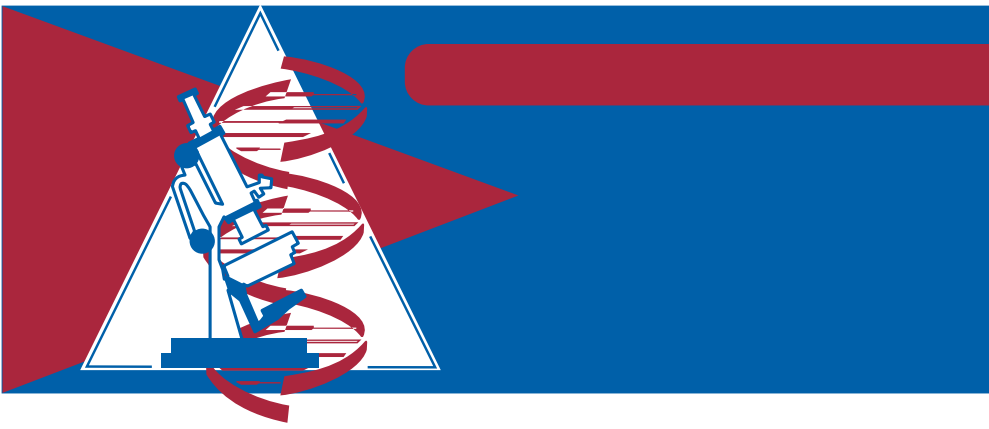
Once the physician has determined the type of breast cancer, the size and location of the primary tumor, and the extent of the disease, it's time to discuss the various treatment options. The doctor will recommend the course of treatment that he or she believes will provide the best results with the fewest disabling side effects.

The goal of the therapy is to prevent the spread of cancer if the disease is confined to the breast and to minimize the possibility of a recurrence of cancer in the future. For women whose cancer has already spread, the physician will develop a treatment plan that eases any pain or other symptoms. This is called palliative therapy.

Partial or total mastectomy (surgical removal of the breast) offers a good chance of a cure for Stage I and II breast cancers. Surgery may also be successful for some Stage III cancers if they have not invaded other parts of the body. Women with Stage IV breast cancer receive palliative treatment.

WHAT ARE THE TREATMENT OPTIONS FOR BREAST CANCER?

Treatment options for breast cancer (like all cancers) vary with the stage of development that the disease is in. Some form of surgery is almost always part of treatment. This can be as simple as the removal of a small cancerous lump or as



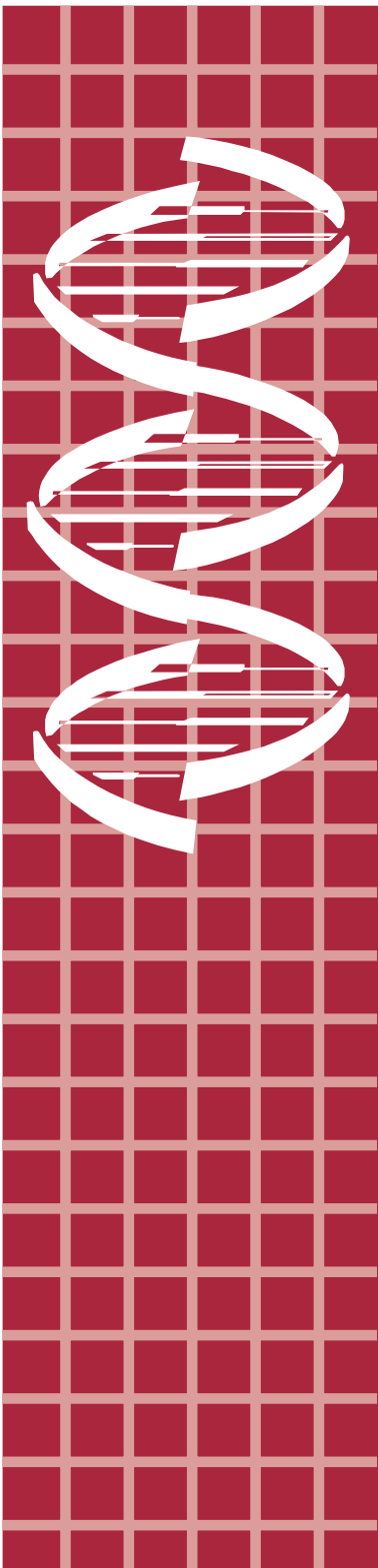
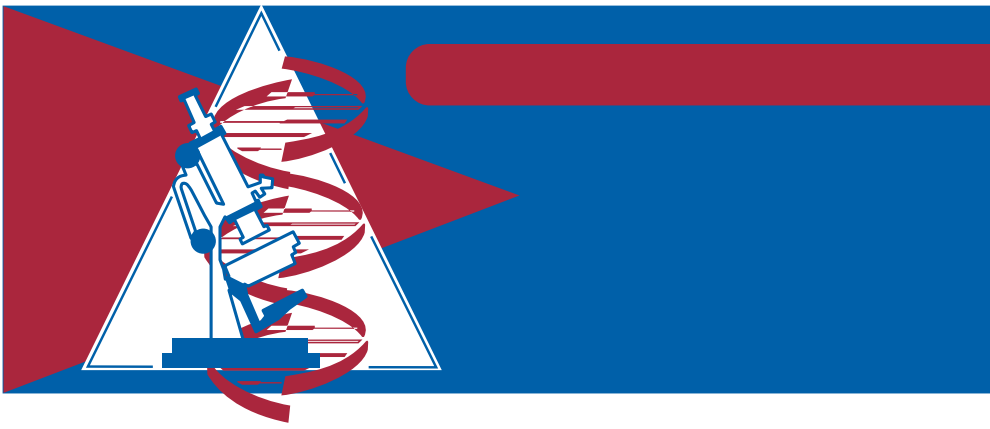
extreme as removing the entire breast, underlying muscle and tissue, and surrounding lymph nodes. Early detection is the key factor that determines what type of treatment is necessary. Treatment options are different for each individual case, but there are several common procedures listed below.

Surgery for breast cancer: Surgery is often followed by radiation, chemotherapy, and/or hormone therapy to destroy cancer cells that may have spread or may have been missed during surgery, this is known as adjuvant therapy.

- **Lumpectomy** – The lump, or tumor, is removed as well as some surrounding tissue. The surrounding tissue can be examined to determine if the cancerous tissue was fully removed in the first surgery. In order to minimize the risk of cancer cells that had spread away from the lump, a 6-week period of radiation treatment commonly follows surgery and some lymph nodes under the arm may be removed.
- **Partial Mastectomy** – the cancer tissue is removed along with a portion of the surrounding breast tissue and the lining over the chest muscle below the tumor. Some lymph nodes under the arm may be removed and radiation therapy could follow.
- **Total Mastectomy** – The entire breast is removed, but the underlying muscle is left intact. Radiation therapy may follow surgery.
- **Modified Radical Mastectomy** – The entire breast is removed as well as the lining over the chest muscles, many of the underarm lymph nodes, and sometimes a portion of the muscles in the chest wall. Radiation treatment could follow surgery. This is currently one of the most common types of treatment for breast cancer.
- **Radical Mastectomy** – The entire breast is removed along with the underlying chest muscle, and all the lymph nodes under the arm. Radiation therapy could follow surgery. Today, this procedure is normally only used when the cancer has definitely spread to the chest muscles.

Other treatments

- **Radiation Therapy** – In some cases X-rays can be used to kill or shrink cancer cells at the site of the tumor. The radiation may also be administered by a machine, such as a linear accelerator or cobalt apparatus, or from a radioactive source implanted within the diseased area. External beam radiation therapy uses radiation from outside the body to focus on the cancer and is, therefore, not the primary treatment for cancer that may have spread.



- **Chemotherapy** – Drugs are administered by mouth or injection to kill the cancer cells. The drugs enter the blood stream and can, therefore, reach areas of the body where the cancer may have spread.
- **Hormone Therapy** – Some types of breast cancer have receptors that are affected by different hormones. In these cases, hormone replacement, hormone alteration, or removal of certain hormone production organs (i.e., ovaries) can be a treatment option. This is not a treatment option for all types of breast cancer.
- **Clinical Trials** – There are always new experimental treatments being tested that often have promising results. The effectiveness and side effects of clinical trials are not always known, but they can sometimes offer hope of survival.

WHAT ARE THE SIDE EFFECTS OF THE TREATMENTS?

Certain side effects have been associated with different types of treatments. Each patient's response to treatment will be different but there are some common effects.

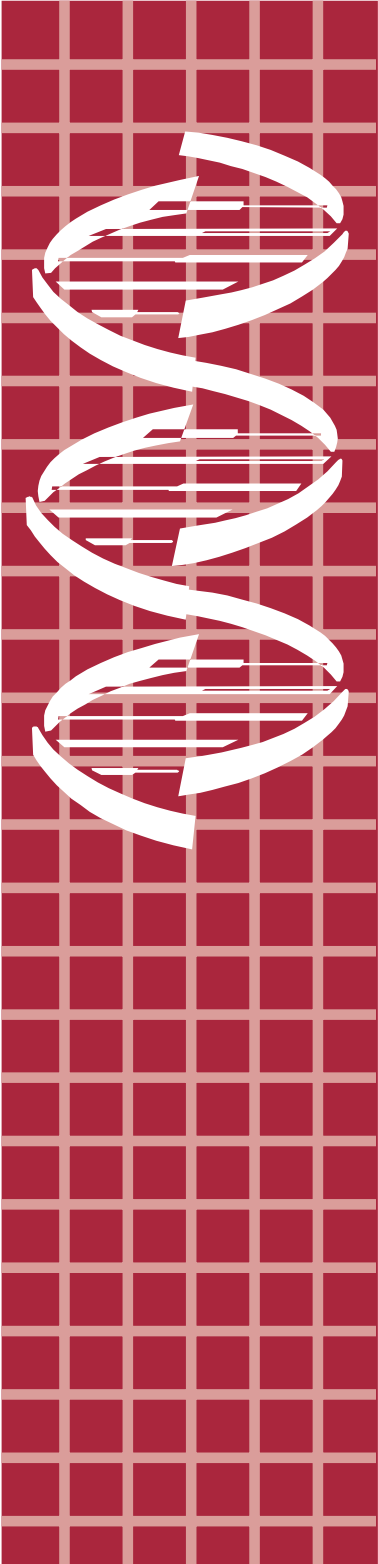
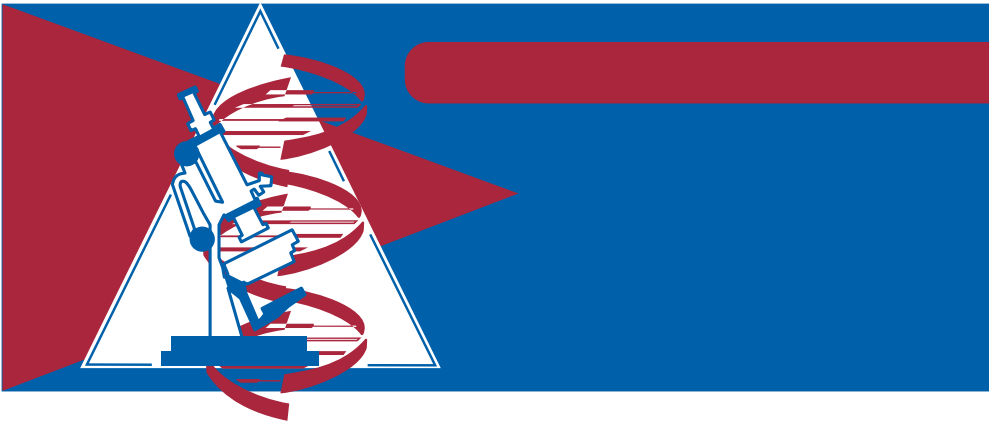
Possible side effects from surgical treatment

- **General**
 - Temporary swelling and tenderness
 - Hardness from the scar tissue at the surgical site
 - Breast disfigurement (can be corrected through breast reconstruction)
 - Possibility of wound infection or internal bleeding at wound site
- **If lymph nodes under arm are removed**
 - Swelling of arm if underarm lymph nodes are removed
 - Limitations in arm and shoulder movement
 - Numbness of upper inner arm

Possible side effects from non-surgical treatments

**Most side effects are temporary and can often be relieved with medication.*

- **Radiation Therapy**
 - Occasional fatigue
 - Swelling and heaviness in the breast (6-12 months)
 - Skin changes similar to a sunburn at affected site (6-12 months)
 - Breasts can possibly become smaller and firmer after treatment
 - Can contribute to swelling of the arm if axilla (underarm) is irradiated after surgery



- **Chemotherapy**

- Nausea and vomiting
- Loss of appetite
- Loss of hair
- Mouth sores
- Increased susceptibility to infection
- Premature menopause (permanent)
- Infertility (can be temporary or permanent)

- **Hormone Therapy**

- Depends on the specific medication used and the individual patient
- Ask your physician about possible side effects before beginning treatment