# BENIGN BREAST DISEASE and BREAST CANCER TUTORIAL

**The information provided on this website is background material only and not treatment recommendations. Treatment decisions should be made by patients and their physician.**

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**NOTE: The abstracted references are available by clicking on the reference.**

**Pathology examples and links leading to a more detailed discussions are accessed by clicking on the highlighted word or term.**

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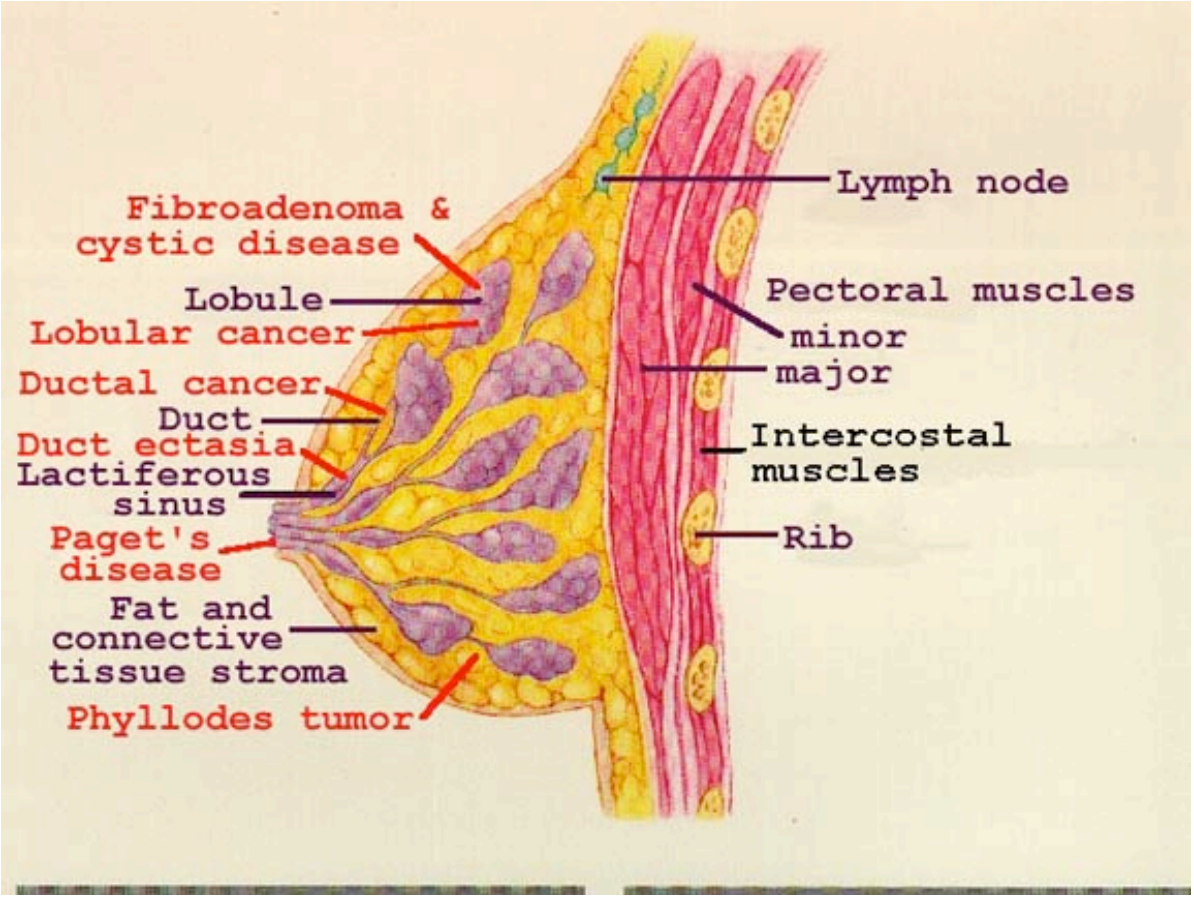
## Normal Breast Anatomy and Physiology

**Breast anatomy and location of disease processes**

The breast glandular tissue consists of 15 to 20 lobules that enter into branching and interconnected ducts. The ducts widen beneath the nipple as lactiferous sinuses and then empty as 5 to 9 nipple openings. Click here for histology. The lobules are comprised of acini that consist of layers of two types of cells (epithelial and myoepithelial) that surround a lumen. Click here for acinar histology.




The primary lymphatic drainage is to the axillary lymph nodes and the secondary lymphatic drainage is to the internal mammary nodes. This is reflected in the lymphatic spread of cancer. In the absence of axillary lymph node metastases, the internal mammary nodes were involved in 13% of medial cancers and in 4% of lateral cancers.

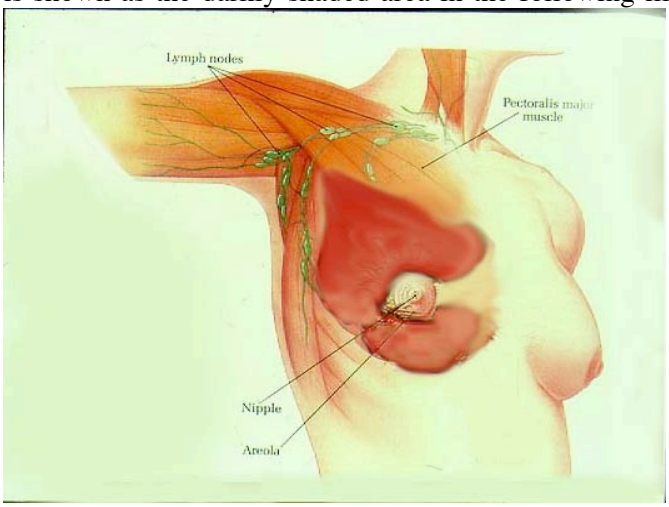
## Normal breast development and physiology

- At **puberty** the breast develops under the influence of the hypothalamus, anterior pituitary, and ovaries and also requires insulin and thyroid hormone
- During each **menstrual cycle** 3 to 4 days before menses, increasing levels of estrogen and progesterone cause cell proliferation and water retention. After menstruation cellular proliferation regresses and water is lost.
- During **pregnancy** cellular proliferation occurs under the influence of estrogen and progesterone, plus placental lactogen, prolactin and chorionic gonadotropin. At delivery, there is a loss of estrogen and progesterone, and milk production occurs under the influence of prolactin.
- At **menopause** involution of the breast occurs because of the progressive loss of glandular tissue.

## Breast examination. Click HERE for complete instructions on how to do a breast examination.

Breast examination should be done 7 to 10 days after beginning menses.

1. **Inspection**- look for dimpling and nipple deformity
2. **Axilla** - 1 to 2% of breast cancers initially present as enlarged axillary lymph nodes
3. **Palpation**
    1. Patient supine with her hand behind her head
    2. Examine from across the table, i.e., right breast from the left side of the table
    3. Distinguish glandular tissue from breast fat
       The breast consists of a mixture of firm glandular tissue and soft fatty tissue. There is a deficit of glandular tissue under the nipple-areolar complex. A typical distribution of glandular tissue is shown as the darkly-shaded area in the following illustration.




    4. Check for loss of pliability as well as for masses

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## Presenting symptoms of breast cancer % of total

- Painless breast mass _ 66
- Painful breast mass _ _11
- Nipple discharge _ _ _ _9

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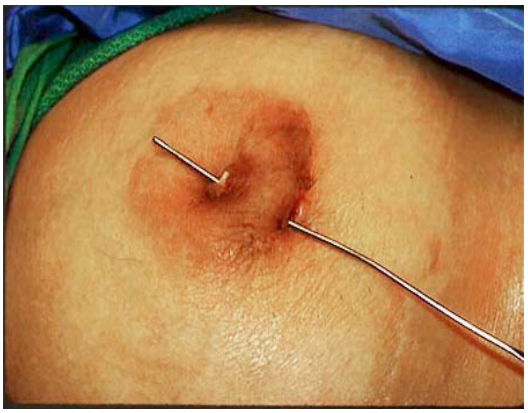
## Differential diagnosis of a breast mass

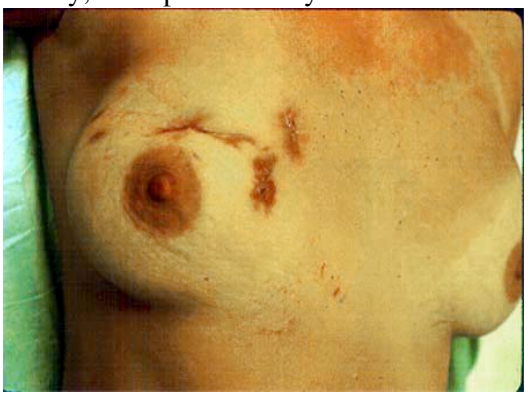
### Benign

- Fibroadenoma
    - Usually found in women younger than 30 years.
    - Rounded in outline and easily movable.
    - About 10% will disappear per each year followed in those women who have fibroadenomas verified by fine-needle aspiration and who opt for follow up rather than for removal (37, 38).
    - Is a long-term risk factor of 2.17 for the subsequent development of breast cancer (39).
- "Fibrocystic disease" is an ambiguous term that includes most types of benign breast disease. Autopsy studies show that over half the women have microscopic changes consistent with fibrocystic breast disease. Fibrocystic disease is not premalignant. The following are some **types**:
    - Gross cyst in fibrocystic breast disease
        - Found in women usually in 40's, therefore overlaps CA age incidence
        - Amenable to needle aspiration or ultrasound for diagnosis.
        - Prerequisites for a successful cyst aspiration.
            - Non-bloody fluid is obtained
            - The lump disappears

        - Re-examination 6 weeks later shows no mass.
    - **Fibroadenosis and micro cysts** in fibrocystic disease
        - Found in women in 30's and 40's.
        - Disappears after menopause.
        - Usually diffuse and ill-defined
        - Usually cyclic with menses
            - Painful and prominent before menses
            - Resolves with menses
- **Atypical hyperplasia of the breast**
    - Marked proliferation and atypia of the epithelium, either ductal (27) or lobular (26)
    - Found in 3% of benign breast biopsies
    - Associated with a 13% subsequent development of breast cancer (4x risk factor)
    - Diagnosed by the same criteria as ductal carcinoma in situ but doesn't have all the characteristics necessary to diagnose intraductal cancer.
    - Some may be an under-diagnosed ductal carcinoma in situ.
- **Other benign conditions**
    - Developmental hypoplasia and hypertrophy
    - Phyllodes tumor is a fibroepithelial tumor of unpredictable behavior. About 10% metastasize and this can occur from either histologically malignant or benign phyllodes tumors.
    - Mammary duct ectasia (periductal mastitis)
        - Acute form is the cause of most nonlactational breast inflammation and periareolar abscess formation. It may be sterile but frequently both aerobic and anaerobic bacteria are involved.
          Only one ductal system in one breast is usually involved and it presents as periareolar inflammation. This shows the fistula to the periareolar area. Additionally, there may be further ductal involvement that has to be tracked deeper into the breast

          Rarely, multiple ductal systems are involved.

        - Chronically, it is the most frequent cause of nipple discharge in premenopausal women.
    - Galactocele
    - Fat necrosis

- Breast pain (mastodynia, mastalgia). Chest wall etiology such as arthritis and muscle overuse cause symptoms much more frequently than does mastalgia per se.
  Therapeutically try
  - Caffeine abstinence
  - Other dietary manipulation
  - Danazol
  - Subcutaneous mastectomy done rarely as last resort.
- Papillomas
  - Small (usually smaller than 1 cm.) intraductal growths
  - Frequently cause nipple discharge
  - Have a fibrovascular tissue core
  - May be solitary or multiple.
  - Breasts containing papillomas frequently develop more papillomas and/or cancer. Single papillomas without atypia carry a 3-fold risk factor and carry a 4-fold risk factor when there is atypical hyperplasia in the papilloma (34). Haagensen found 15 of 39 patients with multiple papillomas also had carcinoma.
  - Sometimes may be difficult to determine whether benign or malignant.

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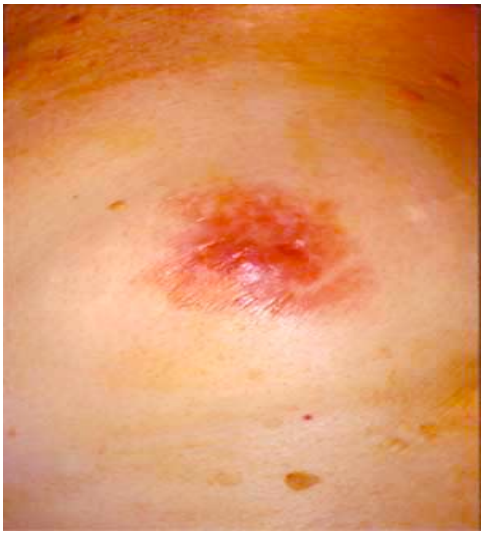
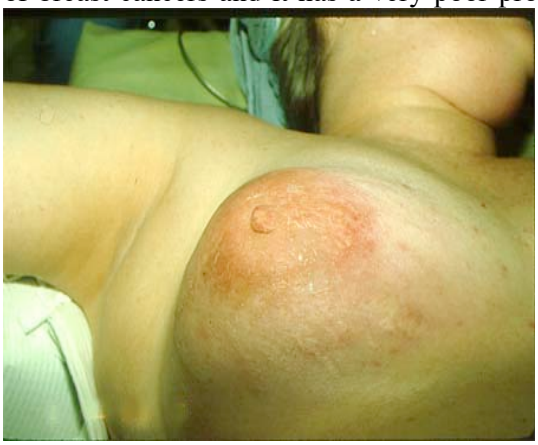
## Non-infiltrating (also called *in situ*) breast cancer. This does NOT metastasize but breast recurrence is a problem. There are two types:

- 1. Lobular carcinoma in situ is usually an incidental biopsy diagnosis. It is an 8 to 10 times risk factor (26) giving about a 1% per year risk for invasive carcinoma in the same or opposite breast. Treatment may be either observation or bilateral mastectomies.
- 2. **Intraductal carcinoma** is being diagnosed with increasing frequency due to mammography. The risk for subsequent invasive cancer is about 1% per year in the opposite breast so the contralateral risk approaches that for lobular carcinoma *in situ*. Recurrence in the same breast varies by type.
  - The old subtypes, based on morphologic criteria, are solid, cribriform, micropapillary, and comedo .
  - Intraductal carcinoma, particularly when of high grade and usually the comedo type, can travel extensively but undetected through the breast. Because of this, there is a risk for the subsequent development of invasive cancer in the breast after the in situ cancer is excised. For this reason, radiotherapy or mastectomy may be indicated after excision of intraductal carcinoma.
  - A classification, developed as a surgical guide, is based on three categories of nuclear grade (low, intermediate, and high) and the presence or absence of necrosis. Recently, age was added as a factor. The Van Nuys grading system serves as a rough guide for treating the breast. However, following these guidelines, there was 0.26% MORTALITY per year from invasive cancer that subsequently developed in the treated breast.
  - Click **here** for a more complete discussion and four cases of in situ carcinoma including an interesting case presenting as nipple discharge.
  - Eventually, intraductal cancer can become invasive.
  - The behavior of low grade ductal *in situ* and lobular carcinoma *in situ* is quite similar.
  - **Paget's disease** is a benign appearing eczematoid lesion of the nipple caused by large malignant cells (Paget's cells) which arise from the ducts and which invade the surrounding nipple epithelium. In the absence of an underlying mass, this lesion is usually due to an intraductal carcinoma. An underlying palpable mass usually indicates invasive ductal carcinoma in which case the prognosis is the same as that for any other invasive ductal carcinoma and is reflected by the status of the axillary lymph nodes.



## Invasive breast cancer.

- Increasing age is the chief risk factor
- Ill-defined outline
- May be associated with skin fixation, dimpling, or nipple retraction.
- The common types of invasive carcinoma are
  - Ductal
  - Lobular
  - Medullary
  - Inflammatory breast cancer plugs the dermal lymphatics and presents with the appearence of infection even though there is not any white blood cell reaction. This cancer accounts for 3% of breast cancers and it has a very poor prognosis.



- **Less common types** (% occurrence). In pure form, these tend to have a relatively good prognosis (24).
  - Mucoid or colloid breast cancer--2.4%
  - Tubular breast cancer--1.2%,
  - Adenoid cystic- breast cancer-0.4%
  - Cribriform breast cancer--0.3%
  - Carcinosarcoma--0.1%
  - Papillary breast cancer
  - Comedo carcinoma
  - Squamous breast cancer
  - Similar to tumors of other organs (e.g., osteoid)
  - Apocrine breast cancer
  - Lipid-secreting breast cancer

- Glycogen-rich breast cancer
- Juvenile breast cancer

## Occult primary breast cancer

- Definition: Adenocarcinoma in an axillary lymph node with histology compatible with a breast primary but with no evidence of a primary tumor in the breast
- Accounts for 1% or less of breast cancer cases
- Survival is at least as good as in patients with an identifiable primary and comparable nodal involvement. I suspect the reason for this is that some of these cancers arise in axillary breast glandular tissue deposits and spread in direct contiguity to adjacent nodes. As such, they are not identifiable as being separate from the node.
- With axillary dissection and no breast treatment, 50% of patients will manifest a breast primary within 5 years. A significant number of the **nonrecurring** cases had a primary tumor in the axilla which was in close proximity to the involved axillary node and which was removed with the axillary surgery. In one series (References\104212.htm), 85% of cancers eventually appeared in non-treated breasts. No breast treatment is therefore NOT an option.
- With axillary dissection and breast radiation, 20% of patients will manifest a breast primary within 5 years.
- With axillary dissection and mastectomy, the literature reports that a primary will be found in 75% of the mastectomy specimens. However, this figure is much higher than has been my experience. Five of my 854 breast cancer patients had an occult primary. No primary was found in the mastectomy specimen in 4 of these, and a small DCIS was found in one (i.e. primary was found in only 20% of cases). Eventually, one patient manifested an advanced ovarian primary of histology similar to the previously excised axillary node.

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## Nipple discharge

- **Causes**
  - **Duct ectasia** (periductal mastitis) is by far the most common cause in premenopausal women. The discharge may be serous, greenish, or bloody.
  - **Carcinoma,** usually associated with a palpable mass, is the cause in about 10% of women age 55 or older.
  - **In the absence of a palpable mass,** Haagensen noted nipple discharge as the presenting symptom **in only 5** of his personal series of **1669 breast cancer** cases.
  - **Intraductal papilloma** or, less frequently, intraductal papillary carcinoma particularly in postmenopausal women.
- **Diagnosis** (in the absence of a palpable mass)
  - Physical examination
    - The discharge in malignancy can be serous, bloody, or waxy.
    - Benign disease discharge may be either bloody, serous or cloudy.
    - Cancer is unlikely if the discharge is coming from both nipples and/or multiple ducts.
  - Cytologic examination of the fluid is helpful in diagnosing cancer but the sensitivity is only about 50%.
  - Management
    - If the discharge is bilateral and/or from multiple ducts, then it is unlikely to be due to cancer. Check the serum prolactin particularly if a premenopausal patient is having irregular periods.
    - A mammogram should be obtained, the patient reexamined examined in 3 and 12 months and another mammogram obtained in 12 months. Most cancers that produce nipple discharge are in situ and can be seen on a mammogram (32).
    - A microdochectomy can be done if the discharge is bothersome to the patient and is coming from a single duct.

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## Breast Cancer Behavior, general comments

- Breast cancer mortality in the US has been increasing 0.6% per year since 1987. This increase in mortality is occurring despite screening mammography and chemotherapy.
- All breast cancers are different. Some consist of a single cell type that closely resembles normal breast cells while others consist of a great variety of different cells types with different appearances and different behavioral characteristics.
- Tumor growth rates observed by mammograms vary considerably. The average breast cancer can be calculated to have been present in the breast for nine years before it reaches 1 cm. size (95% confidence range of 1.7 to 51 years). Calculations are based on Gompertzian growth, i.e., decelerating growth as size increases.
- When breast cancer kills, it does so because of metastases (spread) to distant sites in the body. Such spread can occur anytime during the cancer's sojourn in the breast before it is detected.
- It is a truism that good cancers don't have the ability to metastasize whereas bad cancers metastasize.
- An experiment in the lowly laboratory mouse helps to define one of the problems encountered in studying human breast cancer (104881). Only a minority of cells obtained from human breast cancers grew in immunocompromised mice. The cancer cells that grew in mice were characterized by specific surface antigens. However, once these cancers began to grow in the mice, many cells without the tumorigenic surface antigen appeared.
- Only a small fraction of cells in any specific human breast cancer may have the potential for undertaking an ultimately fatal metastatic event. Solid human cancers contain both malignant and non-malignant elements. Such tumors are usually minced or otherwise disrupted for laboratory study. Consequently, it is difficult to identify and quantitate the portion of human cancers that may be prognostically significant.
- Any metastases have already occurred by the time the cancer in the breast is removed. Usually these metastases exist as deposits that are too small to be detected by tests.
- At surgery, a cancer cannot be identified as being either good or bad because the factor that enables cancers to spread has not been identified. Imprecise information concerning future behavior frequently is obtained via a number of tests.
- Breast cancers arise from the epithelial cells lining the ducts and lobules. Those that don't penetrate beyond the confines of the ducts or lobules rarely metastasize to lymph nodes or to distant sites. These are called non-infiltrating or in situ breast cancers.
- In order for metastases to develop
  - Lymphatics or blood vessels must be penetrated.
  - The cancer cells must remain viable in transit.
  - The cells must lodge and proliferate at a distant site.
- Cancers with lymph node involvement have the ability to penetrate lymphatic vessels, and those with distant spread have the ability to penetrate blood vessels. Lymph node spread does not necessarily mean blood stream spread. However, a cancer that can spread to the lymph nodes is more likely to possess other bad characteristics than one that does not spread to the nodes.
- Cancers spread from the breast to lymph nodes and from the breast to distant sites, not from the breast to lymph nodes and from lymph nodes to distant sites.
- Cancer cells within the same cancer utilize a variety of different metabolic pathways.
- Some of the cancer cells are inherently resistant to chemotherapy drugs for a variety of reasons. Resistant cells replace drug sensitive cells that are killed by chemotherapy . This is analogous to bacterial resistance to antibiotics.
- Also see below: **Biological Predeterminism Revisited. Tying this all together in the 21st century.**

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## Mass screening for breast cancer.

- **Does mammographic screening for breast cancer decrease breast cancer deaths?** No, according to Gotzsche and Olsen (References\104216.htm). Their metanalysis was prompted because breast-cancer mortality has not decreased in Sweden where screening has been recommended since 1985. In contrast to prior metanalyses where all studies are were lumped together, Gotzsche and Olsen assessed the methodology of the large trials and discarded 6 of the 8 trials because of flawed

methodology. In the two unflawed trials, no improvement in either breast cancer mortality or in overall mortality was noted. Moreover, the lumped-together data from 5 of the 6 flawed trials show that for every 1000 women screened biennially throughout 12 years, one breast-cancer death is avoided whereas the total number of deaths is increased by six.

- Unfortunately, screening mammography does **not** decrease **overall** mortality (42) because mammographically screened women have a higher mortality from other causes. For example, per 100,000 patient years followup, screening saved 6.7 lives from breast cancer at the cost of 40 lives lost from cardiovascular disease.
- False positives are a significant problem with mammograms. 43% of women screened annually for breast cancer for 10 years will have a finding that is not cancer (false positive) but that requires further workup (References\104201.htm).
- The Canadian breast screening study is the best study mammographic study that has been done. In women age 40-49, five annual screening with mammography, breast examination and breast self-examination did not reduce breast cancer mortality compared with a single breast examination and breast self-examination instruction (References\104796.htm).
- Dr. Kopans has been one of the staunchest supporters of screening mammography despite its arguable survival benefit. To his credit, he has thoughtfully developed a model based on sound assumptions positing that for every three breast cancers that reach a 2 cm. detectable size, there are 57 other cancers (39 invasive and 18 in situ) that have not yet reached a detectable threshold (104888). This together with the fact that a cancer can metastasize at any time after it becomes invasive can explain why screening mammography is only minimally effective in reducing breast cancer mortality.
- My position on screening mammography is based on menopausal status rather than age per se. Also note that postmenopausal estrogen replacement results in increased breast density and stimulation of fibrocystic changes. This increases both false positives and false negatives.
  - **Premenopausal:** Screening mammography is not indicated. Even in women "at high risk", mammography should be used with caution because all of the genes implicated in breast cancer are involved in DNA repair and as such are particularly vulnerable to damage from radiation. However, NIH's recommendations have vacillated under political pressure. For a discussion of the evolution of NIH's position recommending mammograms every one or two years click here .
  - **Postmenopausal** (Age 50-69)**:** Screening probably reduces breast cancer mortality albeit slightly. Mammograms every 2-3 years probably are useful particularly to detect in situ cancers.
  - **Age 70 and older:** Studies have failed to demonstrate a survival benefit from screening. This is due, at least in part, to increasing mortality from other causes. Therefore, screening should be individualized based on the woman's general state of health.

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## Identification of high-risk groups

**Age** risk in normal population as **new cases per 1000 women years**.

| **Age** | **Risk** |
|---|---|
| 35-39 | 0.5 |
| 40-44 | 1.0 |
| 45-49 | 1.6 |
| 50-54 | 1.7 |
| 55-59 | 1.9 |

Life probabilities with **two first degree relatives** having breast cancer is **15%** for example in the sister of a breast cancer patient whose mother or sister had breast cancer. The risk is 25% if either had bilateral breast cancer. Cancer in 2nd degree relatives increased risk only slightly (10).

## Risk of Breast Cancer is influenced by endogenous estrogen levels

- In premenopausal women, about 60% of circulating estrogen is from the ovaries in the form of estradiol. The remaining 40% is estrone formed primarily in the adipose (fat) tissue via aromatization of androstenedione from the adrenal glands. After menopause, this adipose cell production of estrone is the main source of estrogens and the level of estrone is maintained approximately at premenopausal levels.
- Blood sampling in women age 35-65 years showed **higher** levels of estrone, total estradiol, and free estradiol, and lower level of estradiol bound to sex hormone-binding globulin in women who developed **breast cancer** than in women who remained free of breast cancer (17).
- Many risk factors are related to the **duration of estrogenic stimulation of the breast**.
  - Early menarche and late menopause are positive risk factors.
  - Oophorectomy resulting in early menopause is a negative factor.

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## Postmenopausal hormonal replacement

**Postmenopausal estrogen replacement increases the risk of breast cancer . Virtually all other health benefits can be accomplished by alternative measures.**

- The most significant impact on breast cancer prevention in 2003 was made by two large studies that showed an increased breast cancer risk accompanied postmenopausal hormone replacement therapy. The United States study (Women's Health Initiative) (104884) randomly assigned postmenopausal women to a placebo or an estrogen/progestin hormone replacement group. Halted in 2002 with a mean follow up of 5.2 years, the WHI reported a 24% increase in both noninvasive and invasive breast cancer in the treated group. The cancers in the estrogen/progestin treated women were larger and more advanced than those in the control group. Additionally, the estrogen/progestin treated group had a significantly higher incidence of abnormal mammograms. Although the treated group had an increase in bone mineral density and a decrease in fractures (104895), they also had no benefit and perhaps an increased risk for coronary heart disease (104896), had an increased risk for ischemic stroke (104897), had a slight decrease in cognitive function (104898), and had an increased risk for probable dementia (104899).

  These results were supported by the Million Women Study registry study from the United Kingdom (104894). In this study, on-going hormone replacement therapy was noted and the subjects were followed. Breast cancer incidence data were available for 2.6 years. Compared to the results for individuals not taking hormone replacement therapy, breast cancer incidence was 30% greater for estrogen alone and was double for estrogen/progestin taking patients.

- Mammograms missed breast cancers in 31% of postmenopausal women who were taking estrogens compared with 6% of women who were not taking estrogens. Postmenopausal exogenous estrogens prevent the normal breast glandular tissue atrophy that occurs in the absence of estrogens and decrease the sensitivity of mammography (35).
- Rather than estrogens for **osteoporosis prevention**, other drugs are available such as alendronate (25) or risedronate, raloxifene, or salmon calcitonin that is "sniffed" intranasally. A reasonable threshold for starting such treatments is when bone mineral densities are 2 standard deviations or greater below the mean values that are derived in premenopausal white women.

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## Genetic considerations

- **BRCA1 and BRCA2 are breast cancer genes** that are implicated in **3 to 5%** of breast cancers. Both are familial autosomal dominant. Penetrance by age 70 is 63% for BRCA1 (abnormality on

chromosome 17) and it is associated with ovarian cancer. Penetrance by age 70 is 37% for BRCA2 (abnormality on chromosome 13) and it is associated with male breast cancer. These genes are important in DNA repair.

- The **ataxia-telangectasia gene** predisposes those carrying it to cancer (100 fold in homozygotes). It is autosomal recessive. Heterozygotes (1.4% of population) have a breast cancer risk factor of 5.1 and this is increased by an additional 5.8 times in those having a history of exposure to ionizing radiation (4). Such a condition is **implicated in 10% of breast cancers**.
- Excessive mammograms should be avoided in patients with a strong family history of breast cancer because such patients may harbor genes that increase their susceptibility to radiation induced damage.
- How to manage patients with BRCA1 or BRCA2 patients depends on the patient's perception of risk. Attempts have been made quantify the risk/benefit ratio obtained from various treatment strategies (References\104247.htm).

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## Chemoprevention

Breast cancer is prevented by both tamoxifen(48) and raloxifene(47). Although both prevent breast cancer, they cause complications due to increased blood coagulability, and endometrial cancer in the case of tamoxifen. Moreover, tamoxifen did not decrease breast cancer in 2 of 3 trials. In the successful trial, tamoxifen reduced life-threatening events by only 8.4%.
Raloxifene reduced breast cancer in osteoporotic women but with a much heightened incidence of blood hypercoagulability problems. The increase in pulmonary emoboli (including one fatality) equaled the reduction in breast cancer in raloxifene treated subjects (References\104203.htm).
Therefore, both tamoxifen and raloxifene, if used at all, should be used cautiously for breast cancer prevention since both decrease but don't eliminate breast cancer risk and both are associated with significant complications.

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## Diagnosis of breast cancer

**Breast self-examination (BSE):** The method taught and used for BSE usually is suboptimal. A randomized study to evaluate BSE is now being conducted in Shanghai but the way BSE is taught and the way it is done is open to question. Remember, most breast cancers are found by the patient herself by palpation. I firmly believe in BSE but have noted that it is difficult to teach women to do proper BSE.

BSE has been shown to be efficacious in nonramdomized studies.

- Foster and Costanza (11) found the mean diameter of presenting breast cancers to be 2.5 cm in women doing monthly breast self-examination (BSE) and 3.2 cm in those not doing BSE. **Survival at 5 years was 75% in BSE performers and 57% in non-performers.**
- Le Geyte et al. (13) found **6 year survival of 73.5% in breast cancer patients who were taught and practiced BSE versus 66.1%** in other women (p=0.07).

**Breast ultrasound** can rapidly and accurately determine if a mass is a simple cyst. If so, it is benign and no further work up is necessary.

**DIAGNOSTIC mammograms.** Mammographic interpretation varies widely between radiologists (30) and differs by approximately 53% between maximum and minimum sensitivity. Mammograms are read as benign in 15% of breasts with signs and symptoms of breast cancer and which actually contain a cancer (References\104784.htm). Again, a negative mammogram in a patient with a palpable mass should not dissuade a biopsy or an FNA.

- **Mammography** is a useful adjunctive diagnostic measure when used in patients with clinically

suspicious or high-risk breasts. About 25% of breast cancers diagnosed in mass screening programs are detected by mammography alone. **A negative mammogram should not dissuade biopsy of a suspicious mass.**

**Biopsy:** Biopsy is done to provide cells or tissue in order to establish a definitive diagnosis. Biopsy can be done in several different ways (see below).

**MANAGEMENT OF A MAMMOGRAPHICALLY SUSPICIOUS, NON-PALPABLE LESION. A negative core or FNA should not dissuade biopsy of a mammographically highly suspicious lesion, particularly a spiculated or stellate mass. Conversely, abnormalities that can be *safely followed mammographically* are not biopsied.**

**Method of biopsy depends on available facilities.**

- **The various biopsy methods are as follows:**
    - Needle-directed (guide wire directed) excisional biopsy
        - The gold standard
        - Facilities are widely available
        - Most invasive method
        - Questionable area is completely excised or at least extensively sampled
    - Core needle biopsy
        - Tissue obtained via at least a 14 gauge needle is interpretable by widely available pathologists
        - Less invasive than needle-directed excisional biopsy but more so than fine needle aspiration
        - The lesion is followed if the biopsy is benign and
            - unless it is mammographically very suspicious
            - or if the patient desires removal
        - A cancer may be underdiagnosed because the lesion is not removed
    - Fine needle aspiration
        - Least traumatic since the sample is obtained via a 23 gauge needle
        - Sample interpretation requires specialized expertise
        - The lesion is followed if the biopsy is benign and
        - unless it is mammographically very suspicious
        - or if the patient desires removal
        - A cancer may be underdiagnosed because the lesion is not removed

**Localization** can be obtained either stereotaxically or by ultrasound.

- Stereotaxic localization. Requires special equipment and is time-consuming.
    - Almost all mammographically identified lesions, including microcalcifications, can be localized.
    - If biopsies are done, each biopsy of the lesion requires a separate puncture.
- Ultrasound localization

- Equipment is widely available and localization takes little time.
- Not all lesions seen on mammograms can be visualized with ultrasound.
- Imaging is in real time so the needle can be seen to actually enter the lesion.
- Multiple areas of the lesion can be sampled through the same puncture.

**Comment:** With many calcifications (more than about 30) and a non-mass lesion, it is often difficult to remove all the calcifications even with a needle directed surgical excision. Therefore, extrapolation is required whether a sample is obtained by a core needle biopsy or by surgical excision. Non-mass lesions consisting of few (less than about 30 microcalcifications) are most reliably treated by needle-directed excisional biopsy unless all the calcifications are removed by the core biopsy procedure. In such cases, the sensitivity of core biopsy is about 85% unless all calcifications are removed. In addition to missing some cancers, patients with remaining calcifications have justifiable psychological concerns.

**Algorithm:**

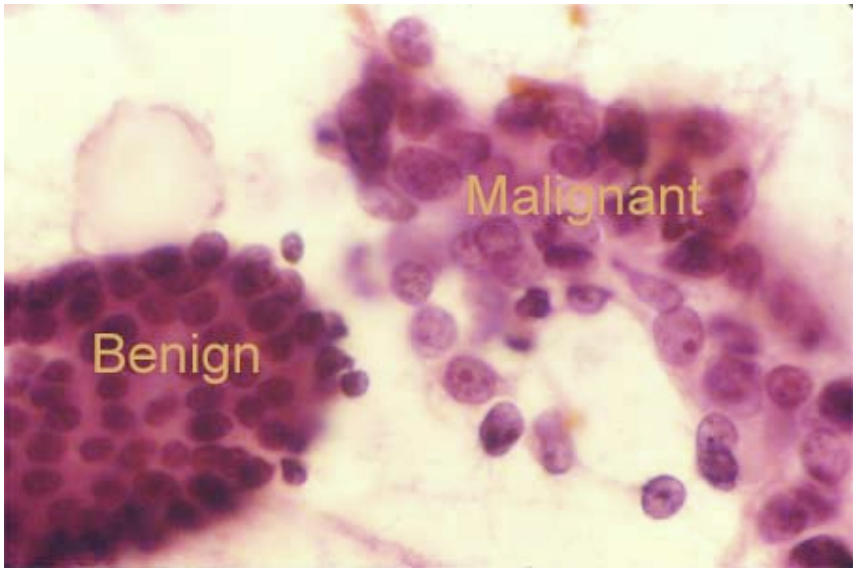
- Mass seen on ultrasound
  - Simple cyst. Mammogram in one year or aspirate.
  - Cyst with debris. Aspirate for cytology
  - Solid. FNA
    - Unsatisfactory. Core or surgical excision.
    - Benign. Repeat ultrasound in 3 months and ultrasound or mammogram in 1 and 2 years unless patient wants it excised.
    - Malignant. Surgical excision.
- Mass not seen on ultrasound. Stereotaxic core or surgical excision. Mammogram in 6, 12, and 24 months if the core is benign.
- Calcifications
  - Fewer than 30. Surgical excision unless all can be removed by multiple stereotaxic cores. (note: sensitivity of 85% is reported for the usual stereotaxic biopsy.)
  - 30 or more calcifications. Stereotaxic core.
- Architectural distortion. Surgical excision.

Note: 1.Lesions diagnosed as atypical hyperplasia on core biopsy should be surgically excised. 2.Lesions diagnosed as in situ cancer should be surgically excised and histologically examined to determine if there is an invasive element.

## Fine needle aspiration

- Examination of cells obtained from solid masses may be diagnostic. If cytologic expertise (41) is available, breast masses can be diagnosed by fine needle aspiration**.**

  This is a fine needle aspirate of a breast mass that contains both benign (left) and malignant (right) cell clumps. The benign clump consists of small, uniformly sized and shaped cells arranged in a single layer of tightly adherent cells. The few cells coming off the clump are devoid of cytoplasm. The malignant clump is thicker and is dyscohesive. The cells are larger and vary in size and shape. Cells come off the clump with intact cytoplasm. The nuclear chromatin is clumped in the malignant cells and is uniform in the benign ones.




Distinguishing between benign and malignant cells is not always as easy as in this example. Computers will help to cytologically diagnose cancer.
In the absence of cytologic expertise, ultrasound can distinguish between simple cysts that can be followed and solid masses should be excised.

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## Breast Cancer Prognosis determination is important for making 1)medical treatment decisions and 2) life-planning decisions.

- **Death rate** from breast cancer is 4% per year
- **Contralateral breast cancer** occurrence rate is 0.7 to 1% per year.

- **Prognosis based on tumor size and lymph node status.** These are the parameters that are used by medical oncologists to make recommendations regarding adjunctive chemotherapy. Some groups have such a good prognosis that adjunctive therapy causes more harm than good whereas the converse is true in other groups. Since treatment decisions are based chiefly on axillary lymph node status, we should examine what axillary lymph nodes tell us.

    - **30 Year** Relative Survival: **negative nodes=62%**, **positive nodes (N1)=19%** (24). Note that about 40% of node-negative patients die of breast cancer and 20% of node-positive patients are still alive after 30 years. From this standpoint, lymph node involvement is not an accurate prognostic feature.

    - % 5-year relative survival (24,740 cases)(12)

Size (cm) _ _ _ _ _ _ _ _ _ <2 _ _ _ _ _ __2-5_ _ _ _ _ _>5

Negative nodes _ _ _ _ _ _96.3 _ _ _ _ _ _ 89.4 _ _ _ _ 82.2

1-3 positive node _ _ _ _ _87.4 _ _ _ _ _ _ 79.9 _ _ _ _ 73.0

=>4 positive nodes _ _ _ _66.0 _ _ _ _ _ __58.7 _ _ _ _45.5

The statistical difference between these groups is highly significant, but clinically there is considerable overlap.

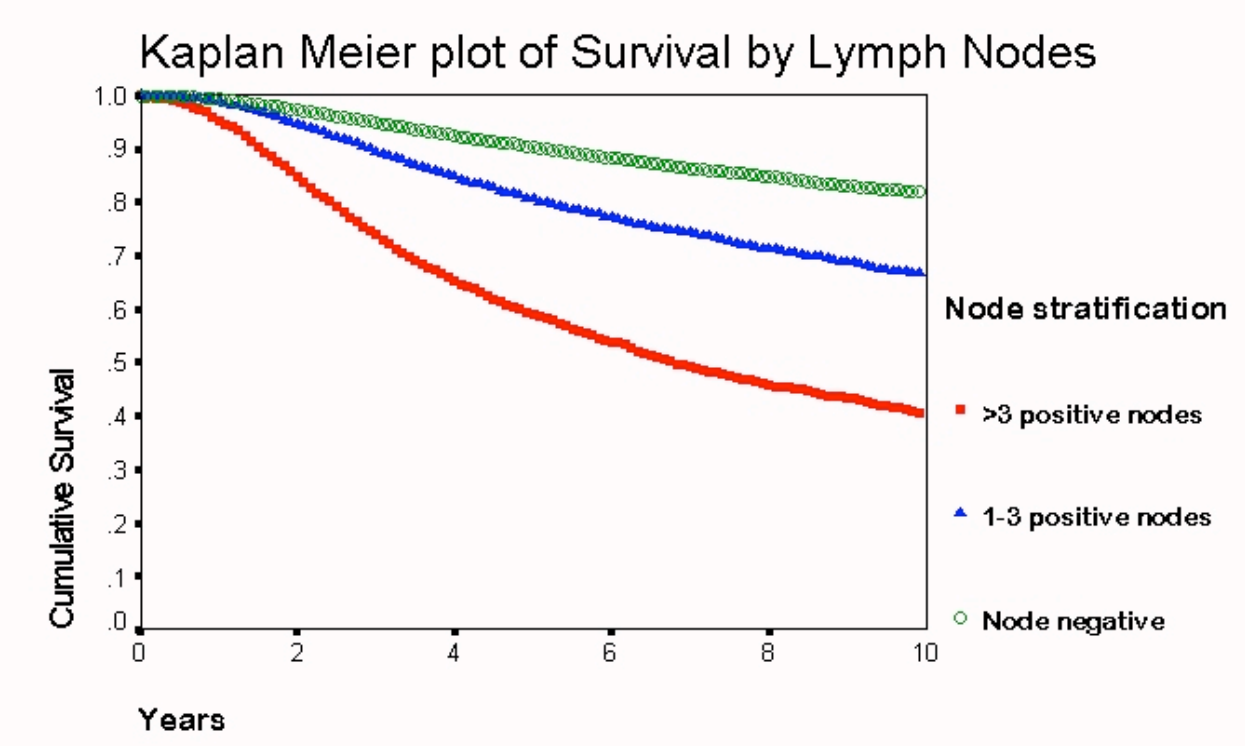
- Prognosis of patients with only a microscopic tumor focus in a lymph nodes is the same as that in node negative patients (References\104787.htm, References\104797.htm).

**The following is a detailed discussion of the lack of prognostic estimations based on lymph node status. These data provide the basis for the hypothesis that there are inherently "good" and "bad" breast cancers.**

**Background:** Axillary lymph node invasion by cancer is generally considered to be the strongest prognostic feature for breast cancer . Usually, axillary lymph nodes are surgically removed to determine the extent of invasion since many treatment decisions are based on this finding. In the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute, five-year survival was 91% in node negative (N0), was 81% in the 1-to-3 node positive (N1), and was 59% in the greater-than-3 positive node groups (N2). There appear to be three possible explanations for the survival differences:

- that all cancers within a particular nodal group are **similarly aggressive** with those in the N0 group being the biologically the least lethal and the N2 cancers the most lethal
- that N0 cancers are **detected the earliest** and the N2 cancers the latest
- all three groups contain the **same number of lethal cancers** but these are diluted by many more inherently nonlethal cancers in the N0 group than in the N2 group.

The distinction between the three possibilities is not conveyed by the conventional Kaplan-Meier chart.

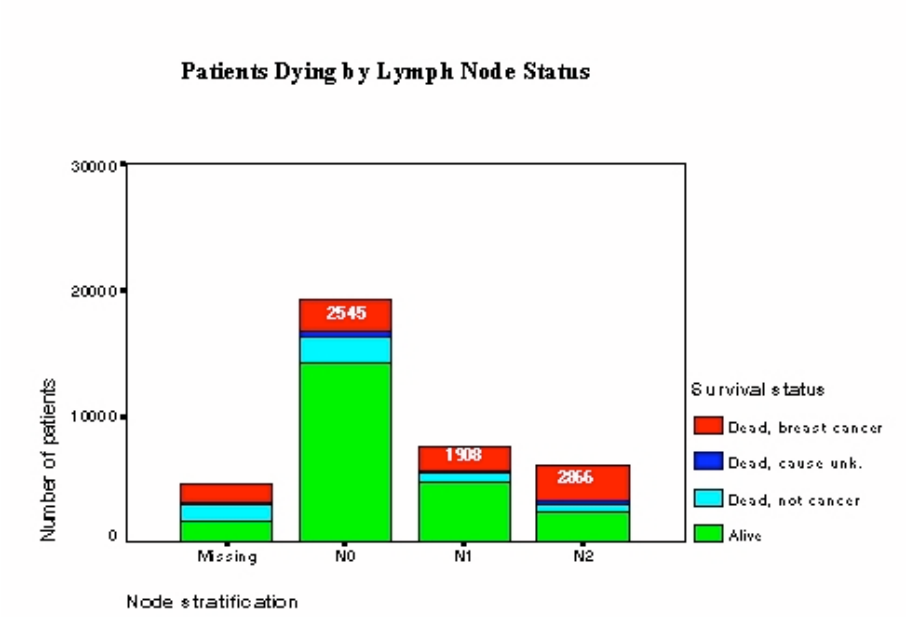



The purpose of this work is to determine which of the three options is correct.

**Methods:** Statistical analyses were done on breast cancer cases obtained from the SEER database that contains information on 37,000 invasive breast cancer cases that presented without distant metastases and which were collected between 1977 and 1982.

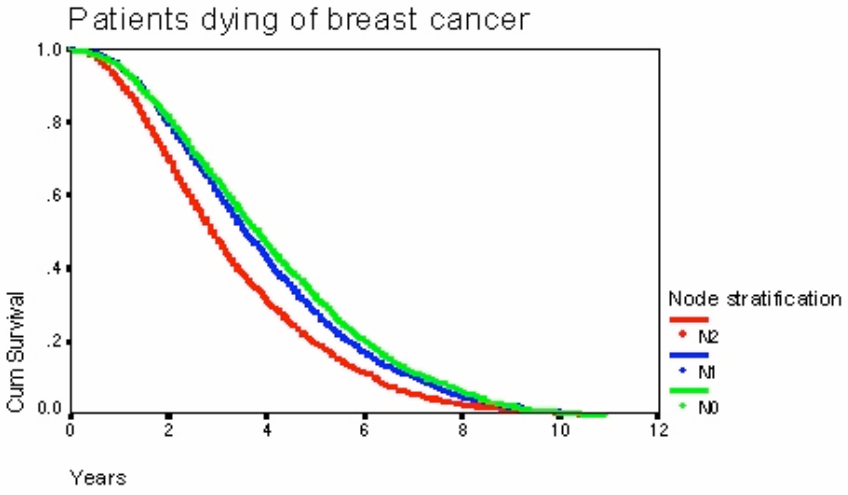
**Results:** In the SEER data, the **same absolute number of patients died from breast cancer in**

**the N0, N1, and N2 groups of patients**. However, there were more patients who did not die of breast cancer in the N0 group than in the N1 group. In turn, there were more patients who did not die of breast cancer in the N1 than in the N2 group. This is graphically shown in a bar graph where it is apparent that the same number of deaths occurred in all nodal groups.




In actual numbers, as many patients died whose lymph nodes were negative as did patients who had positive nodes. The tops (red) show that the same number of patients died in each of the three lymph nodal groups but the bottoms (green) show that there are more patients that did not die in the N0 than the N1 than the N2 groups.

The patients died at the same rate (fraction of patients in each group that died each year) as is shown below:




From this is concluded that there are the same number of biologically bad cancers in all three groups, but these are diluted by the most good cancers in the N0 group and the least in the N3 group. Additionally, the patients who died did so at the same rate. One must conclude that the axillary lymph node status reflects the prevalence of lethal cancers in patients falling within a particular nodal stratification. The nodal status **does not** reflect the lethality of cancer in any specific patient within a particular stratification.

- **Prognostic estimation based on histologic tumor features**
  - Differentiation: The more a cancer's cells look like normal cells, the more likely it is to be a non-aggressive cancer. Cancers that are "well-differentiated" look and act most like normal cells. About 90-95% of women with these cancers will be cured with surgery. Unfortunately, less than 9% of breast cancers are well differentiated. Poorly differentiated cancers look least like normal cells. They are more likely to be aggressive. Moderate differentiation is in between. Most breast cancers have moderate or poor differentiation.
  - The type of cancer. This is most helpful in uncommon cancer types. Some, like inflammatory, nearly always are aggressive. Others like mucinous, tubular, cribriform, and papillary usually are non-aggressive cancers.
  - Nuclear grade. The nucleus is the center of the cell. It is where a cell first starts to divide. If many cells are getting ready to divide or are in the process of dividing at one time, it is probably a rapidly growing tumor. Rapidly growing tumors are more likely to be aggressive. There are many ways of classifying nuclear grade, but the lowest number usually is the best.
  - Vascular Invasion: Under the microscope, one can see cancer cells inside the blood or lymph vessels. Cancers that get into the blood stream are more likely to spread to other parts of the body. They almost certainly get there. The real question is, can they grow there?
  - With recent progress in image analysis, the assessment of computer-derived histological

features is becoming attractive. Studies have shown such analyses to be as prognostically accurate as are those based on tumor size and lymph node status (104890), (104891) but do so without axillary surgery.

- **Prognostic estimations based on "markers"**
  - Whether or not estrogen and progesterone receptors are indicative of the cancer's aggressiveness is arguable.
  - Markers such as S-phase, ploidy, and HER-2/neu have inconsistently been shown to be related to prognosis. It is usual to find one of the hormone receptors low and/or one marker elevated when a prognostic "panel" is done on a breast cancer. No one knows how to weigh any of these markers either alone or in combination. However, both hormone receptor status and HER-2/neu are extremely important in designing future therapy.

**Biological Predeterminism Revisited. Tying this all together in the 21st century with gene arrays.**

In the 18th century the concept was developed that breast cancer began as a local disease and spread first by lymphatics to axillary nodes and then from the nodes to distant sites by way of the blood stream. This concept was not questioned until the 20th century. This concept became the basis for the Halsted radical mastectomy and its variations, some of which were more and others less radical. The concept of initial lymphatic spread was laid to rest by the NSABP B04 study which found equivalent survival in the three arms of the study: simple mastectomy, simple mastectomy plus regional nodal radiotherapy, and Halsted radical mastectomy. Thus, the concept of early removal of the axillary lymph nodes as a means to affect a cure became untenable.

In the 1950s, Ian Macdonald espoused the concept of biological predeterminism. He observed that 56% of patients with cancers 1 cm. or smaller versus 77% of those with cancers larger than 5 cm had axillary metastases. In other words, a size differential of 4 cm. was important in only 21% of breast cancer patients. He presagefully stated, “The factors determining the inherent potential of a given neoplasm for growth and dissemination are probably genetic.” Shortly thereafter, Black described certain microscopic characteristics that were related to prognosis. These findings advanced the idea that certain inherent characteristics of individual breast cancers were related to prognosis.

The concept that all breast cancers were the same was again questioned in the 1960s when chemotherapy drugs were developed. Varying responses were observed in patients who had microscopically identical cancers. My work showed that tumors often utilize different metabolic pathways to accomplish cell division. Chemotherapy sensitivity or resistance is determined by which pathway is used. Moreover, even the same cancer contains populations of cells that have greater or lesser amounts of the critical enzymes. Chemotherapy kills the drug-sensitive cells leaving the resistant cells unscathed to divide and replace drug-killed cells. Hence, initially sensitive cancers eventually become drug-resistant.

The next big leap in our understanding of cancer behavior was based on genomics research. Methods developed in the early 2000s allowed the quantitative assessment of gene expression in various tissues. Reports appeared that showed that early-recurring breast cancers had upregulated cell cycle, invasion, metastasis and angiogenesis genes. Cancers with a propensity to metastasize expressed large amounts of these genes whereas lesser amounts were expressed in those less prone to metastasize. Additionally, similar patterns of gene expression were found in primary cancers and in their metastases. These data contradicted the long-held theory that the malignant potential of cancer cells developed as the cancer grew. It was finally proven that some cancers possess a metastatic potential from their onset.

Since genes control the behavior and appearance of cancer cells, it is not unexpected that genes controlling long-recognized poor-prognostic features such as division, invasion and angiogenesis were upregulated in “bad” cancers and that metastatic gene upregulation strongly correlated with microscopic unfavorable tumor-features. Our microscopic findings demonstrated that morphology, like gene expression, was independent of tumor size and of cancerous involvement of the lymph nodes.

Now, we have sufficient data to mandate reassessment of “early detection” and to question the need for staging axillary surgery. How often does early detection make a difference and why is staging axillary

surgery necessary if comparable information is obtained without? Encouraging as the results gene analyses are, we have to explain why half the patients with a poor-prognostic profile do not recur within ten years and why 15% of those with a good profile do recur. Some of this aberrant behavior can be explained by the unaccounted and variable ratio of stromal to malignant cells present in all cancers. Additionally, non-complying poor-prognostic profile cancers may simply be lying dormant or viable metastatic deposits may never have been established. Additional work needs to be done to refine these findings and to integrate them into our breast cancer treatment algorithms.

References:

Fisher B;Montague E;Redmond C;Barton B;Borland D;Fisher E;et al; Comparison of radical mastectomy with alternative treatments for primary breast cancer. A first report of results from a prospective randomized clinical trial. Cancer 39:2827-2839,1977.

Black,M.M.; Opler,S.R.; Speer,F.D. Survival in breast cancer cases in relation to the structure of the primary tumor and regional lymph nodes Surg Gynec Obst 100:543-551,1955.

MacDonald I; Biological predeterminism in human cancer Surg Gynec Obst 92:443-452, 1951

Wolberg, W.H. and Brown, R.R. Autoradiographic studies of in vitro incorporation of uridine and thymidine by human tumor tissue. Cancer Research 22:1113-1119, 1962.

van't Veer, L.J., Dal, H., van de Vijver et. al. Gene expression in profiling predicts clinical outcome of breast cancer. Nature 415:530-536, 2002

Bernards R. Weinberg RA. A progression puzzle. Nature. 418(6900):823.

van de Vijver MJ ;He YD; van't Veer LJ; Dai H; Hart AAM; Voskuil DW; Schreiber GJ; Peterse JL; Roberts C; Marton MJ; Parrish M; Atsma D; Witteveen A; Glas A; Delahaye L; van der Bartelink H; Rodenhuis S; Rutgers ET; Friend SH; Bernards R; A gene-expression signature as a predictor of survival in breast cancer. New England Journal of Medicine 347(25):1999-2009,2002.

Ramaswamy S;Ross KN;Lander ES;Golumb TR. A molecular signature of metastasis in primary solid tumors. ; Nature Genetics 33:49-54, 2003.

Wolberg,W.H.; Street,W.N., Computer-generated nuclear features compared with axillary lymph node status and tumor size as indicators of breast cancer survival. Human Pathology. 33(11):1086-1091,2002.

- **Prognostic estimation based on gene profile**
  Another *potential* way to avoid axillary dissection is by the assessment of gene expression profiles in the primary cancer (104889), (104882). At this date, such assessments do not appear to be more prognostically accurate than those results obtained from lymph node status but do so without axillary surgery.

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## Role and type of definitive surgery in breast cancer

- Results of National Surgical Adjuvant Study (15) indicated comparable cure rates from Halsted **radical** mastectomy (removing breast, axillary lymph nodes, and chest wall muscles), **total mastectomy** (removing the breast) **plus radiation** therapy to the lymph nodes, and **total** mastectomy without any axillary lymph node treatment. In the latter case, axillary node removal was done when and if palpable adenopathy occurred. This study showed that removing non-palpable axillary lymph nodes, even if they contained cancer, did not improve survival. Therefore
- **Axillary node dissection or sampling is done to estimate prognosis** rather than to effect cure. Options include
  - Complete axillary lymph node dissection which frequently (about 20%) causes arm problems

consisting of varying degrees of lymphedema. This should be done if lymph nodes contain cancer.
    - Sentinel lymph node sampling consists of preoperatively injecting a blue dye and/or a radioactive colloid material into the breast so lymph nodes draining the breast can be identified and removed for histologic examination. Sentinel lymph node biopsy as a means to avoid complete axillary dissection is coming into wider use. Veronesi et al (104885) found similar results in clinical stage 1 patients assigned to either sentinel node biopsy alone followed by complete dissection but only if a sentinel node were positive compared with sentinel node biopsy plus routine complete axillary lymph node dissection.
    - Anatomical five-node biopsy of the axilla (References\104783.htm).
    - Observation alone if axilla is clinically negative. This does not adversely affect prognosis but precludes pathologic staging.
- Role of **less than mastectomy with radiation therapy** in the primary treatment of primary breast cancer.
    - **Rationale:** The curability of breast cancer is limited by its propensity for distant metastases. The primary breast cancer can be controlled in several ways including local excision and radiation.
    - **Procedure:** The primary tumor is excised surgically, 2 cm or smaller-Milan (16), 4 cm or smaller-NSABP (14). Radiation is started 10 days later. 5000 r is given to the breast over 5 weeks with an additional 1000 r boost to the area of the primary tumor.
    - **Why is breast radiation needed?** Breast radiotherapy after tumor excision reduces breast recurrence at eight years from 40% to 10% (14). In a different study, after ten years, in patients with small, node-negative cancers, the breast recurrence was 14.4% **in radiated** and was 16.1% in non radiated breasts (19). **Therefore**, tumor excision alone may be considered for selected node-negative patients with small cancers.
    - **Advantages:**
        - Excellent to good **cosmetic** results in 2/3 of patients.
        - **No demonstrable difference in long-term cure rate** to that of mastectomy. (14), (16).
    - **Disadvantages:**
        - **Local failure** rate of 1-2% per year requiring subsequent mastectomy *(Note: breast recurrence does not affect overall cure)*.
        - 7% of local recurrences are unresectable (i.e. about 1% of total breast conservation cases will fail with unresectable local recurrences by 10 years).
        - Requires 6 to 8 weeks in **treatment** versus one 1 week from surgery.
        - **Late sequelae** (breast fibrosis, rib fractures, breast edema and late carcinogenicity).
        - The NIH series noted that 77% of the women treated with conservation had **undesirable local symptoms** compared with 25% of those treated with mastectomy (9).
        - **Expensive**. The radiotherapy aspects cost $16,000 in 1995 dollars.
    - **Brachytherapy vrs. whole breast radiation after lumpectomy.**

      Brachytherapy consists of implanting radioactive seeds in the area of the lumpectomy in order to increase the dose of radiation to the tumor bed. This has theoretical advantages and disadvantages. Since 85% of the breast recurrences occur in the same quadrant as the original cancer (14), it makes sense to maximize the radiation to the local area and to spare the rest of the breast (note: this usually also is done as a local boost with external beam therapy). How important is high-dose local treatment in the case of small cancers with ample surgical tumor-free margins?

      In favor of external beam therapy is the fact that the original cancer can spread remotely through the breast ducts. In that context, external beam therapy makes the most sense.

The percentage of women opting for mastectomy or for tumor excision plus breast irradiation seems to vary geographically. A higher percentage of women are treated with tumor excision plus breast irradiation at both coasts, than in Wisconsin. In Wisconsin, approximately one-half of patients with primary breast cancer are considered candidates for breast conservation and half of those eligible elect conservation (20). Click here for medical considerations for breast conservation. Those who elect conservation have more concern about body integrity whereas those who elect mastectomy have more concern with the radiation (18). However, patients are satisfied with their treatment decision and have similar psychosexual

adaptation (21).

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# Adjunctive therapy

## Adjunctive radiotherapy after mastectomy

Many studies have failed to demonstrate a survival benefit derived from giving radiotherapy to node positive patients following a modified radical mastectomy. Articles from Canada and Denmark published in 1997 demonstrated a significant survival benefit from postoperative radiotherapy. However, the incidence of local-regional recurrence after mastectomy reported in these studies was extremely high. Beyond this, neither study defined the frequency of follow-up evaluations.

Surgery should be done in such a manner so local-regional recurrence is minimized. Should local-regional disease occur, its early detection optimizes the likelihood of completely eradicating local recurrences, which may affect survival. These considerations prevent the application of the results of the Canadian and Danish studies to other population groups. The extremely high rates of local-regional recurrence encountered by these groups needs to be explained before routine radiotherapy can be recommended to patients who have undergone mastectomy. Click here for a more detailed discussion.

## Adjunctive drug therapy after breast cancer surgery

The purpose of drug treatment given at the time of surgery (adjunctive therapy) is

- to delay recurrence and
- to increase overall survival.

Now, we will explore the history and the underlying data that supports adjunctive therapy.

Drugs that caused debilitating metastatic breast cancer to regress were developed in the 1950's. 5-Fluorouracil was developed at the University of Wisconsin. As a resident, I was involved in the initial clinical trials. Never before had such favorable results been obtained from drug treatment in patients with metastatic breast cancer.

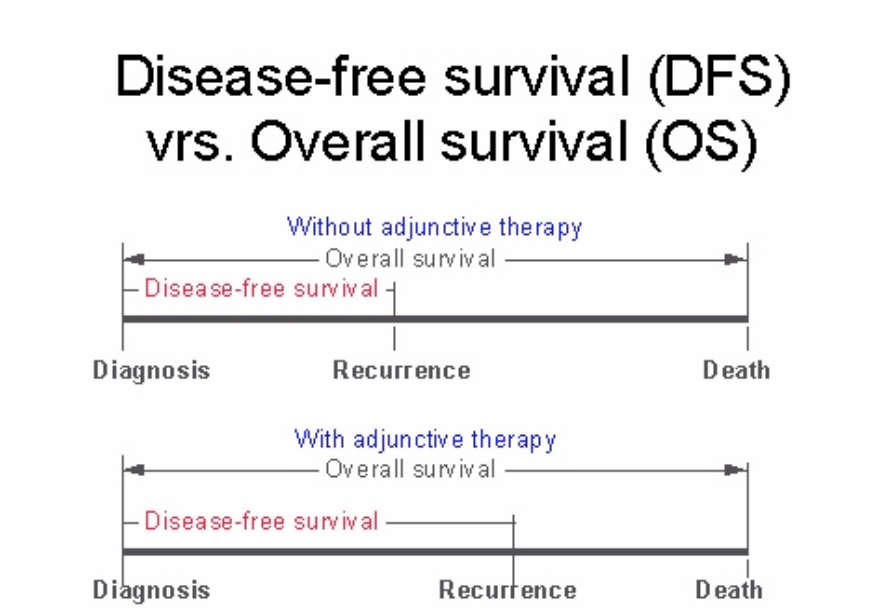
Soon such drugs were given at the time of surgery in hopes of increasing cancer cures. Compared with non-treated control patients, the combination of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) given at the time of surgery so significantly delayed recurrence (References\101909.htm) that, based on results obtained with other drugs in leukemia patients, it was assumed that survival would also be increased. The authors noted "First of all, not enough time has yet elapsed to indicate whether the difference in the rate of recurrence can also affect the rate of survival, which remains, in our opinion, the ultimate goal of adjuvant therapy." The study was terminated and ultimately only 59% of control patients were given combination chemotherapy at the time of first relapse. At 10 years the survival was 44.8% in controls and was 59% in the adjunctively treated patients (References\102797.htm). Patients in both groups continue to die even after 10 years. A **13 patient** survival swing between treated and control survival at 10 years would have resulted in a null result. Unfortunately, since that time it has been considered unethical not to treat node positive women adjunctively.

The reasoning behind NOT having a placebo group in adjunctive trials is reasonable but the subsequent course of events should be kept in mind.

- Although prolongation of survival is unclear, there is no doubt that adjunctive chemotherapy delays recurrence if recurrence is destined to occur. Adjunctive chemotherapy is "beneficial" in that sense. Therefore, trials were designed to compare new regimens verses those that had been used previously (CMF for ECOG and L-PAM for NSABP). Still, treatment given at the time of relapse, specifically crossover treatment, was not specified in protocols. Consequently, overall survival assessments continue to be hazy.

- The majority of breast cancer patients want everything possible to be done.
- Adjunctive chemotherapy soon became standard even for off study patients.

Still, it is not clear whether adjunctive chemotherapy actually increases survival. Two events **may** happen following breast cancer diagnosis.....cancer recurrence and death from cancer. The time between diagnosis and recurrence is referred to as **disease-free survival (DFS)** and the time between diagnosis and death as **overall survival (OS)**. Drugs given immediately after cancer is diagnosed are referred to as **adjunctive therapy**. As was shown above, adjunctive therapy increases DFS, i.e., delays the recurrence if the cancer is destined to recur. Adjunctive chemotherapy clearly **decreases** survival after recurrence (References\104770.htm). Studies have not clearly shown that overall survival is increased more by giving treatment at the time of surgery as opposed to waiting to see if the cancer recurs and treating when and if the cancer recurs.




In the 1990's it became fashionable to use a statistical method called meta-analysis in order to group many studies together in hopes of giving a clear answer to questions that were not clearly answered by the individual studies. Meta-analysis showed that overall survival was increased when adjunctive therapy was given. This study was published in 1992 in Lancet and shows the overall survival at 3 years (left) and 5 years (right) of the world-wide adjunctive therapy experience. The vertical dotted line indicates no change in survival between treated and non-treated patients, a dot to the left indicates that treated patients died sooner than did non-treated ones, and a dot to the right indicates that non-treated patients died sooner. The length of the horizontal bars indicates the 95% confidence limits of the studies.

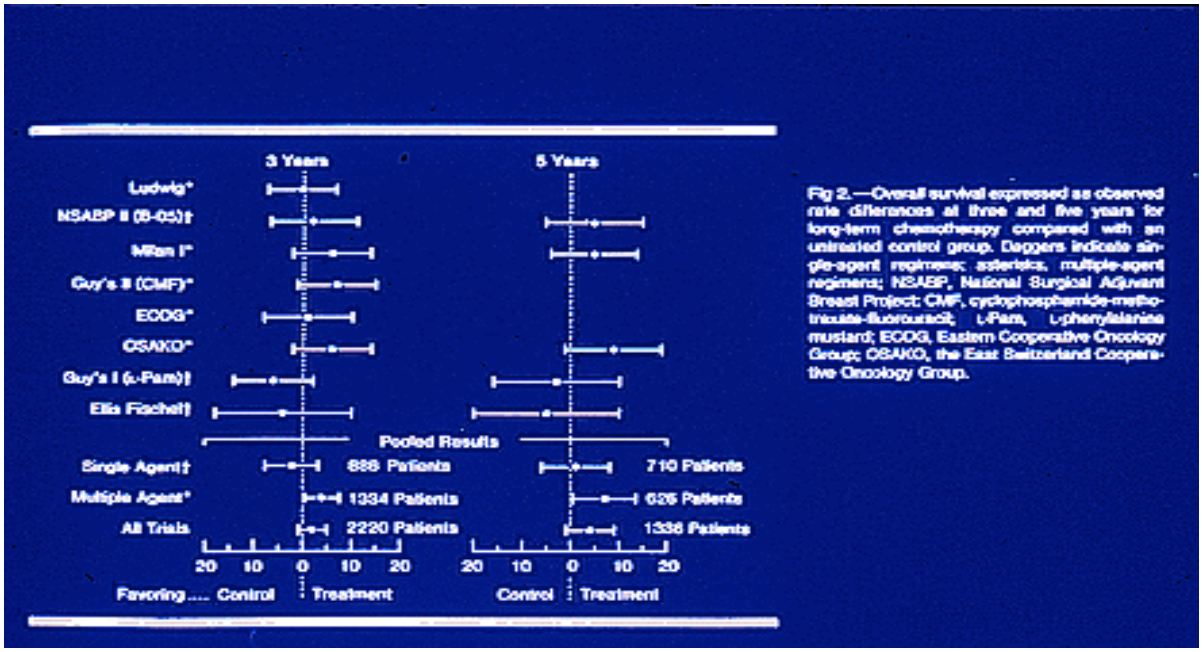



Fig 2.—Overall survival expressed as observed rate differences at three and five years for long-term chemotherapy compared with an untreated control group. Daggers indicate single-agent regimens; asterisks, multiple-agent regimens; NSABP, National Surgical Adjuvant Breast Project; CMF, cyclophosphamide-methotrexate-fluorouracil; L-Pam, L-phenylalanine mustard; ECOG, Eastern Cooperative Oncology Group; OSAKO, the East Switzerland Cooperative Oncology Group.

The technique of meta-analysis has been questioned since one-third of the time different results were obtained by meta-analyses and by large prospective randomized trials. Particularly vulnerable to misinterpretation were meta-analyses in which the results of individual studies fell on either side of the null (vertical) line.

An additional very important consideration concerning the adjunctive trials in breast cancer has never been adequately defined. This is whether the patients who did not receive adjunctive therapy at the time of surgery (controls) received comparably effective treatment when their cancer recurred. If they did not receive effective treatment when the cancer recurred, then it is highly probable that those who received treatment at the time of surgery would live longer than did those who never received such treatment. Thus, adjunctive therapy would appear to cause patients to live longer.

In summary, the overall survival benefit of adjunctive therapy is not tremendous and is not needed in patients who are destined to survive anyhow. Unfortunately, it is not possible to predict if or when breast cancer will recur.

Despite these reservations, chemotherapy with its side effects is routinely recommended to adjunctively node-positive patients and to those with large primary cancers. A meta-analysis shows the effect of **adjunctive chemotherapy** on reducing **annual odds of death**. (7), (8). First, we need to understand what is meant by "reducing annual odds of death". For the first four years after surgery, the death rate in control patients was 7.47% per year and for patients given adjunctive polychemotherapy it was 6.40% per year. Although the rate of death in patients who received chemotherapy was reduced by about 1% per year, the data are reported as a 14% (1.07 / 7.47) reduction of the annual odds of death.

**Tamoxifen**

Age <50, premenopausal _ _ _ _ _ _ _ _ _6% SD 5

Age 50-59, postmenopausal _ _ _ _ _ _ _19% SD 4

Age 60-69 _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ 17% SD 4

Age 70+ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _21% SD 6

**Ovarian ablation**

Age <50, premenopausal _ _ _ _ _ _ _ _28% SD 9

**Polychemotherapy**

Age <50, premenopausal _ _ _ _ __ _ _ _25% SD 6

Age 50-59, postmenopausal _ _ __ _ _ _13% SD 7

Age 60-69 _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _10% SD 6

Age 70+ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _Too few studies

This analysis indicates that in postmenopausal women adjunctive tamoxifen should be used rather than polychemotherapy and in premenopausal women ovarian ablation is as effective as is polychemotherapy. The place of adjunctive therapy has been reviewed (28) . An additional unresolved question is whether adjunctive chemotherapy given to premenopausal women is attributable to more than its ovarian ablative effect (6). Response seem to be most favorable in those premenopausal women experiencing chemotherapy-induced ovarian failure but, unfortunately, such women also experience rapid and significant decreases in bone mineral density (References\104769.htm).

Survival benefits from adjuvant polychemotherapy appear to be greatest in node-positive women younger than age 50 and to be least in node-positive women age 50-69(46). An overview by Cole et al. (References\104770.htm) found that overall chemotherapy-treated younger women gained an average of 10.3 months of relapse free and **5.4 months** of overall survival within ten years compared with the no-chemotherapy group.

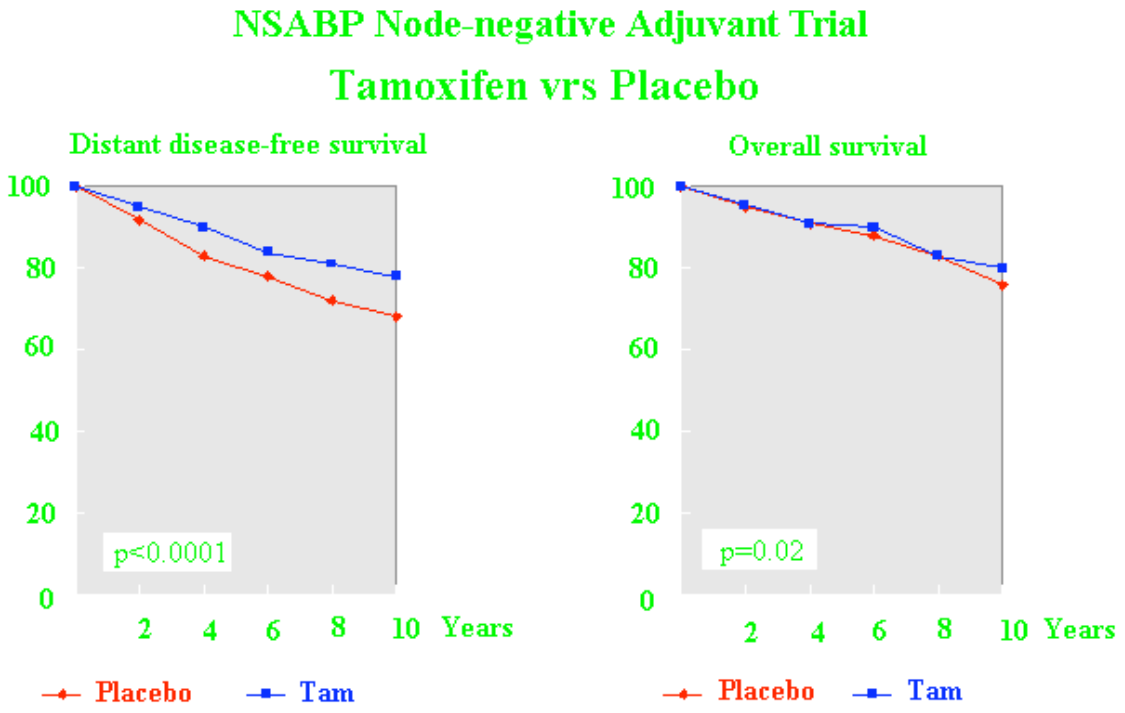
How much survival time is adjunctive chemotherapy worth? The answer to this question was referred to in the above article (References\104770.htm). A study was done with a time trade-off method to obtain patients' preferences from 104 women who had received adjuvant treatment with cyclophosphamide plus methotrexate plus fluorouracil. Patients in that study were presented with hypothetical scenarios of the general form: "Suppose that without treatment you would live 5 years. Based on your experience of chemotherapy, what period of survival would make 6 months of initial treatment worthwhile?" 46% of the patients would accept the chemotherapy for as little as 6 additional months' survival time, and 77% would accept it for an additional 12 months

Patients are willing to take adjunctive therapy despite the modest survival benefits (29). Because of the modest benefits, the therapy's side effects should be carefully weighed against the possibility of the cancer's recurring particularly in node-negative patients.

The function of adjunctive chemotherapy in node negative breast cancer is defined by the NSABP node negative trial comparing placebo with tamoxifen (40) . This trial is noteworthy because 1) there is a placebo control and 2) the same treatment (tamoxifen) or comparable treatment probably was given to patients in the placebo group when distant recurrence was found.

The results are reported for two endpoints

- Distant disease-free survival that is the duration between surgery and the appearance of metastases in distant organs such as bone or lungs.
- Overall survival that is the duration between surgery and death.




The results show that the appearance of distant metastases was delayed by starting tamoxifen immediately after surgery, but this had a negligible effect on survival. In other words, after recurrence tamoxifen prolonged survival longer in the placebo control patients (those who did not receive tamoxifen immediately after surgery) than in those patients who were already receiving tamoxifen.

Aromatase inhibitors are gaining a place in chemotherapy for **postmenopausal** women. After menopause, estrogen is no longer produced by the ovary but still is produced from androstenedione and testosterone by aromatase enzymes. Estrogen may reach many times higher levels in breast cancer cells than are detectable in the blood of postmenopausal women. Anastrozole and letrozole are commonly used examples of drugs that block aromatase (see 104883 for a review).

Letrozole reduced recurrence ($p<=0.001$) compared with placebo in postmenopausal women who previously had received five years of tamoxifen adjunctive therapy (104900). Unfortunately, the trial was prematurely terminated based on the recurrence data. At the time that the trial was terminated, there was no significant survival difference between the adjunctively letrozole treated and the placebo group of patients. The still-outstanding question is whether or not giving adjunctive treatment is better than a wait-and-see course and withholding of treatment until recurrence is demonstrated.

The results of other adjunctive chemotherapy treatments in other patient sets probably are similar. **Unless the treatment goal is to delay the time of recurrence rather than to prolong survival, it is difficult to justify treating patients having a good prognosis immediately after surgery rather than waiting and treating only those in whom cancer recurs.**

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## Self-help questions

## Case management problems

- **In situ cancer. Management of 4 cases.**
- **Work up of a breast mass in a premenopausal woman.**

How to do a breast examination and self examination

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