# CHAPTER 5. BENIGN BREAST DISEASE IN WOMEN

**Richard J. Santen MD,** Professor of Medicine, University of Virginia Health System, Charlottesville, Virginia 22908;

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## INTRODUCTION

Benign breast disease in women is a very common finding. An understanding of the hormonal and growth factor control of breast development and function is key to the rational and systematic evaluation and treatment of patients. A firm understanding of benign breast disease is important since sequential steps are necessary to distinguish benign from malignant conditions. This chapter will review the physiology of breast function, provide histologic examples of common lesions, and detail practical approaches to evaluation and treatment.

## BREAST PHYSIOLOGY IN WOMEN

Hormones and growth factors act upon stromal and epithelial cells to regulate mammary gland development, maturation and differentiation (1). Broadly summarized, estrogen mediates development and elongation of ductal tissue; progesterone facilitates ductal branching and lobulo-alveolar development; and prolactin regulates milk protein production. At puberty, estradiol and progesterone levels increase to initiate breast development. A complex tree-like structure results and comprises 5 to 10 primary milk ducts originating at the nipple, 20 to 40 segmental ducts, and 10 to 100 sub-segmental ducts ending in glandular units called 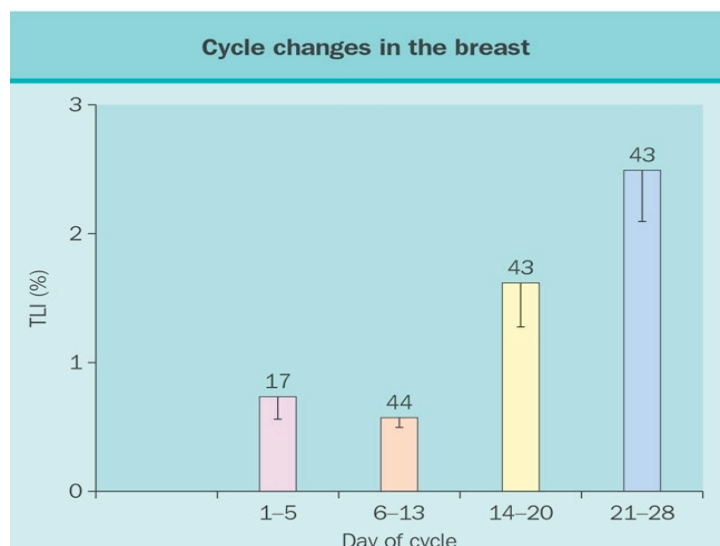terminal duct lobular units (TDLUs) (2). During the menstrual cycle the increments in estrogen and progesterone stimulate cell proliferation (Figure1) and during the luteal phase apoptosis occurs (3). As a consequence, the breast can increase by as much as 15% in size during the luteal phase.



**Figure 1.** Influence of the cycle phase on breast total labeling index (TLI) of women less than 34 years of age (Reprinted with permission from Going JJ, Anderson TJ, Battersby et al. Proliferative and secretory activity in human breast during natural and artificial menstrual cycles. Am. J Pathol. 130:193-204, 1988).
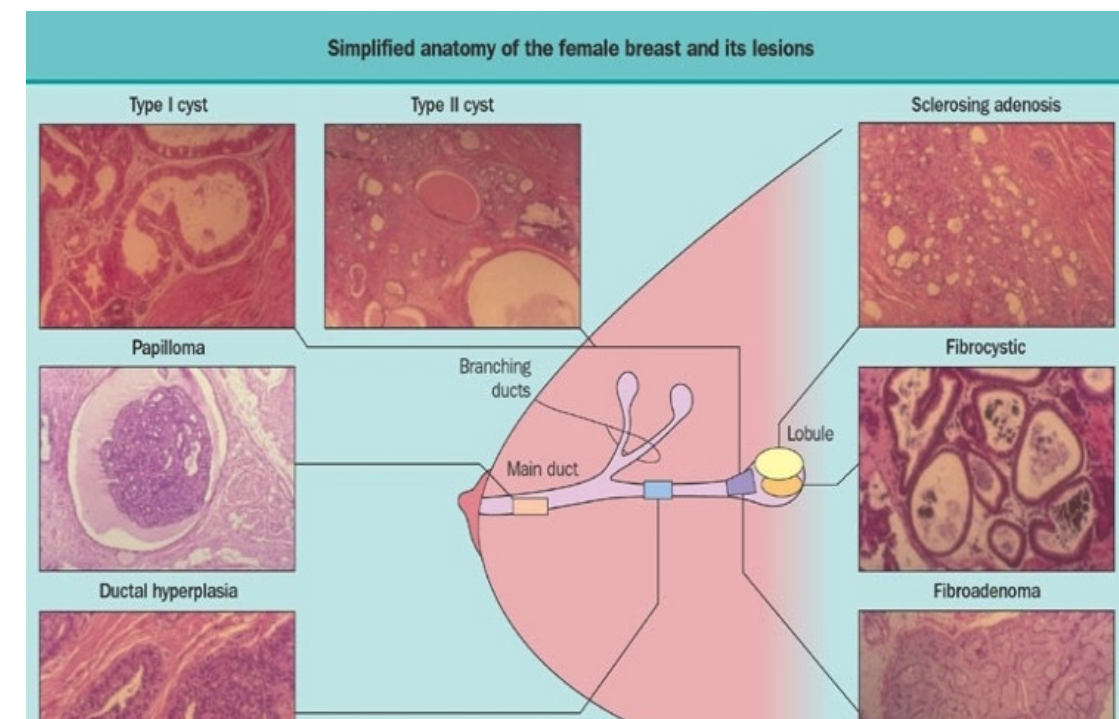
## AGE RELATED CHANGES IN BREAST MORPHOLOGY

The anatomic and histologic structure of



**Figure 2**. Simplified anatomy of the female breast illustrating the major structural components of the breast, the anatomic location of various lesions, and the histology of these lesions and corresponding sites of origin of potential lesions.

the breast undergoes substantial change during the period from early adolescence to menopause (4). The normal histologic appearance represents a spectrum ranging from a predominance of ducts, lobules, and intra- and inter-lobular stroma to patterns with a predominance of fibrous change and cyst formation, a process formerly called fibrocystic disease. The term "fibrocystic changes" is now preferred since up to 50 to 60 percent of normal women may have this pattern histologically (5).  This new term implies that women with lumpy breasts or non-discrete nodules do not have breast disease.  Importantly, fibrocystic changes detected clinically incur no increased risk of breast cancer.

Specific changes in the breast, relating to stromal, ductal and glandular tissue occur as a function of age. As a means of clarifying the changes occurring, we separately consider the reproductive period involved and the specific histologic changes present in stroma, ductal and glandular tissue.  Changes within the normal range are called normal or aberrant and more severe changes are considered to represent disease. A simplified drawing (Figure 2) of the breast illustrates the important structures and the histologic appearance of common lesions.  A schematic diagram (Figure 3) describes the relationship of age to structural changes in the breast leading to benign breast disease.

**Spectrum of benign breast problems**

| Reproductive period | Breast component | Normal | Aberrant | Disease |
|---|---|---|---|---|
| Early Ages 15–24 | Glandular | • Cyclical hormonal effects with mild breast pain | • Fibroadenoma | • Giant or multiple fibroadenomas |
| | Ductal | • Normal | • Normal | • Normal |
| | Stromal | • Normal | • Juvenile hypertrophy | • Uni- or bilateral macromastia |
| Middle Ages 25–34 | Glandular | • Cyclical hormonal effects with mild breast pain | • Exaggerated hormonal effects with breast pain, tenderness, nodularity | • Severe cyclic or non-cyclic breast pain, tenderness, nodularity<br>• Nodules requiring biopsy |
| | Ductal | • Normal | • Normal | • Normal |
| | Stromal | • Normal | • Areas of ill-defined fullness on physical examination | • Firm or discrete area requiring biopsy |
| Late Ages 35–55 | Glandular | • Cyclical hormonal effects with mild breast pain<br>• Microcysts | • Multiple microcysts<br>• Sclerosing adenosis<br>• Lobular hyperplasia | • Lumps requiring biopsy<br>• Lobular carcinoma in-situ |
| | Ductal | • Normal | • Isolated macrocysts<br>• Duct ectasia<br>• Ductal hyperplasia<br>• Discharge | • Multiple macrocysts<br>• Periductal mastitis<br>• Atypical ductal hyperplasia |
| | Stromal | • Normal | • Periductal fibrosis<br>• Nipple retraction | • Lumps requiring biopsy |

**Figure 3:** Classification of the Spectrum of Benign breast problems. Adapted from the ANDI classification (Hughes LE, Mansel RE, Webster DJT. Aberrations of normal development and involution (ANDI): a new perspective on pathogenesis and nomenclature of benign breast disorders. Lancet 2:1316-1319, 1987). It should be noted that this diagram represents concepts in a simplified fashion and does not reflect the complex interplay among the various components.

## Early reproductive period

G*landular* components of the breast may respond to cyclic hormonal stimuli in an exaggerated fashion with the development of single fibroadenomas. These consist of lobular units which grow to larger than normal size and contain both epithelial and stromal elements. Fibroadenomas range in size from slightly larger than a normal single lobular unit to larger, more discrete palpable lesions. The incidence of fibroadenomas peaks at age 20-24. The prevalence on physical examination in young women is 2% in young women but 15-23% when evaluated prospectively at autopsy (6,7).  Fibroadenomas range in size from small to large (i.e. >5cm) with the largest ones (giant fibroadenomas) almost always seen in puberty or pregnancy (Figure 4).

The other components of breast tissue are involved much less commonly in the early reproductive period(8,9). *Ductal* abnormalities are exceedingly rare. *Stromal* hyperplasia may occur and produces juvenile breast hypertrophy or rarely, the more significant problems of unilateral or bilateral macromastia (enlargement of breast tissue beyond what is considered normal).

## Middle Reproductive Years

*Glandular* breast tissue continues to undergo changes in response to cyclic increments in plasma levels of estradiol and progesterone. Some have termed this process of *glandular* change, adenosis. *Ductal* changes
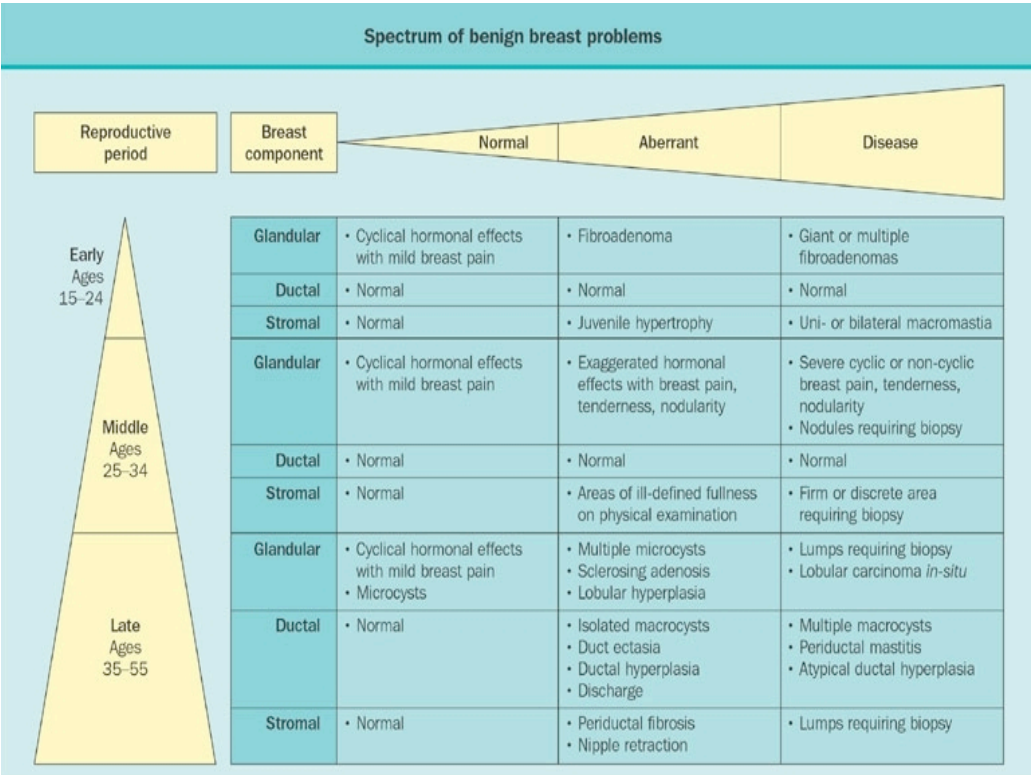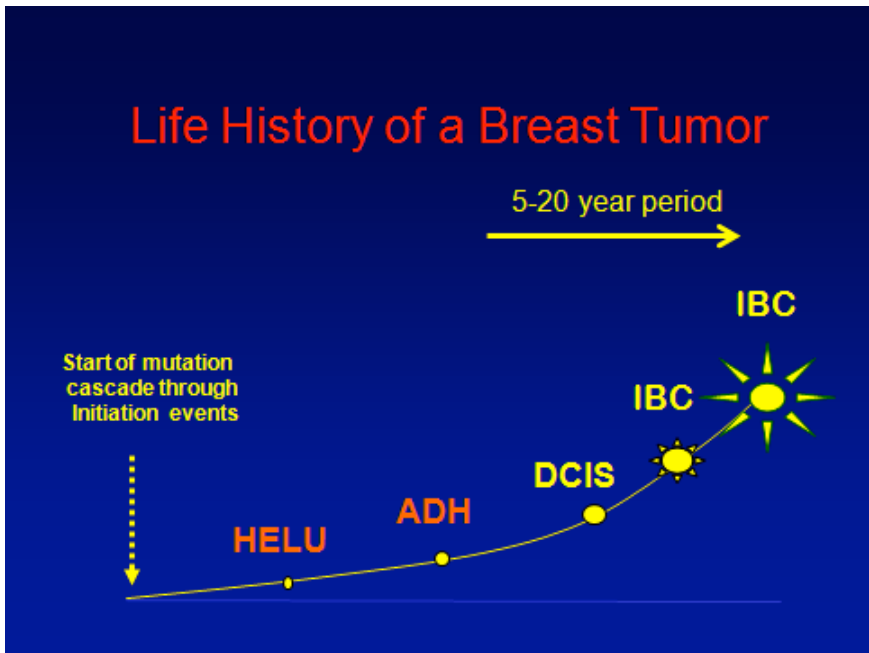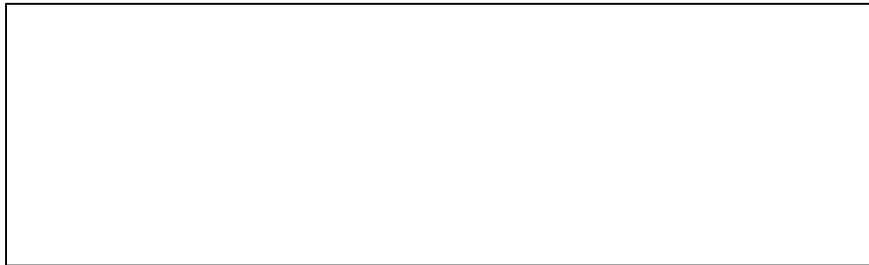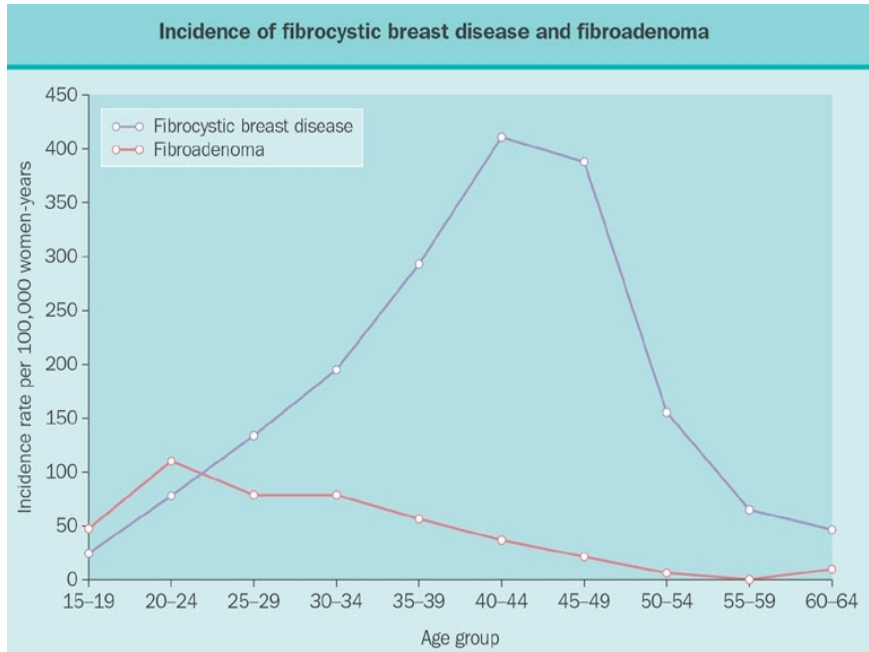
remain uncommon in the middle reproductive period.  *Stromal* hyperplasia may occur which results in areas of ill-defined fullness ("lumpy-bumpy" consistency) on physical exam or in firm areas requiring biopsy.

## Late Reproductive Period

*Glandular* tissue may become hyperplastic with sclerosing adenosis or lobular hyperplasia. The hyperplastic *glandular* lesions may progress to palpable or mammographically detectable abnormalities requiring biopsy. LCIS (lobular carcinoma in situ) may be found incidentally when these lesions are biopsied. LCIS is typically not palpable and rarely (5%) associated with calcifications on mammogram.

*Ductal* tissue also may undergo hyperplastic change with an increase in number of ductal cells but without alterations in their appearance. This later evolves into a condition called hyperplastic enlongated lobular units (HELUs) (10). These are characterized by large lobules approaching 100 μ in diameter. With progression of the HELUs, atypical ductal hyperplasia, or ductal carcinoma in situ (DCIS) may ensue. It should be noted that the concept of HELUs as a precursor of atypical hyperplasia has been controversial and not agreed upon by all experts.  A current theory of carcinogenesis suggests an ordered sequence whereby normal breast tissue progresses to HELUs, atypical hyperplasia, and then to DCIS, and finally to invasive and metastatic cancer (Figure 5). This orderly progression depends upon the number of acquired genetic mutations accumulated by clonal cells in the breast. Recent data suggest that an average of 11 "driver" mutations and 100 bystander mutations are present in established invasive breast cancer (11). Based on the number of mutations required for cancer, current opinion suggests that breast cancer is a process that takes many years to develop, starting perhaps as early as fetal life.  The progression from the earliest changes to invasive breast cancer is considered to take 5-20 years, based upon cancer doubling times of 1-6 months (11A).

Another process, not associated with cancer, involves duct **ectasia**. This is characterized by distention of subareolar ducts and presence within them of yellowish-orange material (Figure 6). Histologically, crystalline oval and round structures thought to be lipid in origin are present. Penetration of the duct wall by this material produces acute inflammatory
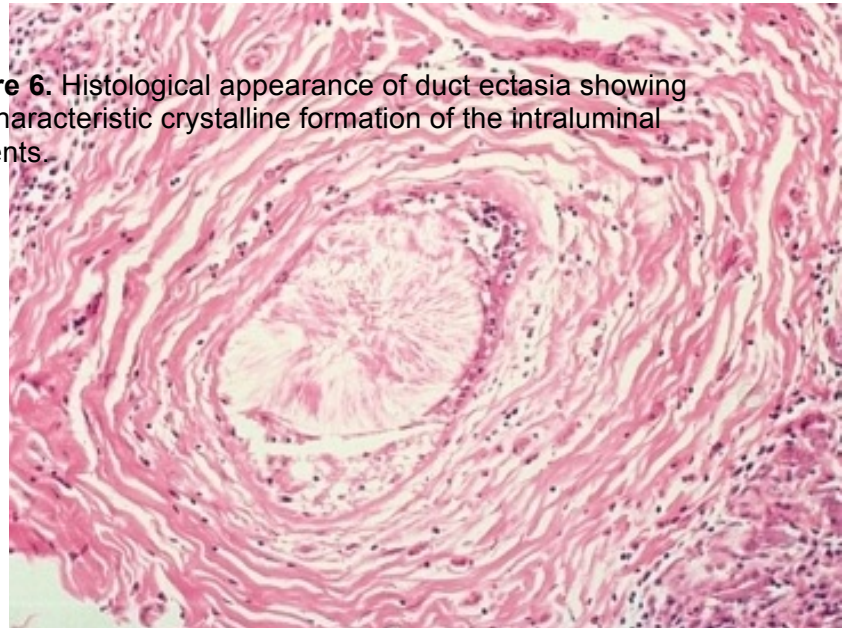


Incidence of fibrocystic breast disease and fibroadenoma



Life History of a Breast Tumor

changes in the surrounding tissues. Spontaneous resolution

Residual periductal fibrosis and nodule formation often persist. Periductal mastitis, a condition thought to be more frequent in cigarette smokers, represents a more chronic and extensive inflammatory process. Abnormalities of ductal secretion may result in discharge of clear, cloudy, blue, green or black aqueous material. Finally, *stromal* hyperplasia can result in nipple retraction or in palpable lesions requiring biopsy to distinguish from breast carcinoma. Histologically, the tissue may contain fibroblasts nearly exclusively, predominantly fibroblasts with admixture of glandular epithelium, or the classic appearance of a radial scar. Some degree of stromal hyperplasia may occur in 50-60% of normal women, particularly those in their middle and late reproductive periods.

**Figure 7.** The percentage of breast tissue which is dense on mammogram is determined by computer assisted analysis and classified as none, <10%, 10-25%, 26-50%, 51-75%, >75%. The relative risk of breast cancer increases with each step of increased breast density. Taken from Boyd et al (13).

# Menopause

Glandular tissue undergoes atrophic change following the menopause and a greater percentage of the total breast is made up of stroma and fatty tissue (i.e. approximately 97%) than present prior to menopause. With use of estrogens alone or estrogens plus progestins as postmenopausal hormone therapy (MHT), ductal and lobular tissue persist and the range of lesions observed during the menopause parallels those seen during the late reproductive period (12).



**Figure 6.** Histological appearance of duct ectasia showing the characteristic crystalline formation of the intraluminal contents.

Breast tissue containing a larger than normal proportion of stromal and glandular tissue appears dense on mammography.

When these lesions are biopsied and compared to areas of low density, they are found to contain a higher proportion of stroma and glandular tissue and lesser amount of fat. Notably, dense lesions contain more of the enzyme aromatase, when quantitated by a histologic score after staining with an aromatase monoclonal antibody (13A). This finding is likely associated with a higher local production of estradiol. Dense breast tissue, if quantitated with a computer assisted method of determining breast density, provides the most powerful means of predicting risk of breast cancer over time (Figure 7).

**ETIOLOGY OF BENIGN BREAST DISORDERS**

Clinical observations in women receiving estrogens and anti-estrogens suggest that hormonal events play a role in the etiology of benign breast lesions. In post-menopausal women receiving estrogens ± progestins for > 8 years, the prevalence of benign breast lesions is increased by 1.7 fold (95 percent CI 1.06-2.72)(14). In the
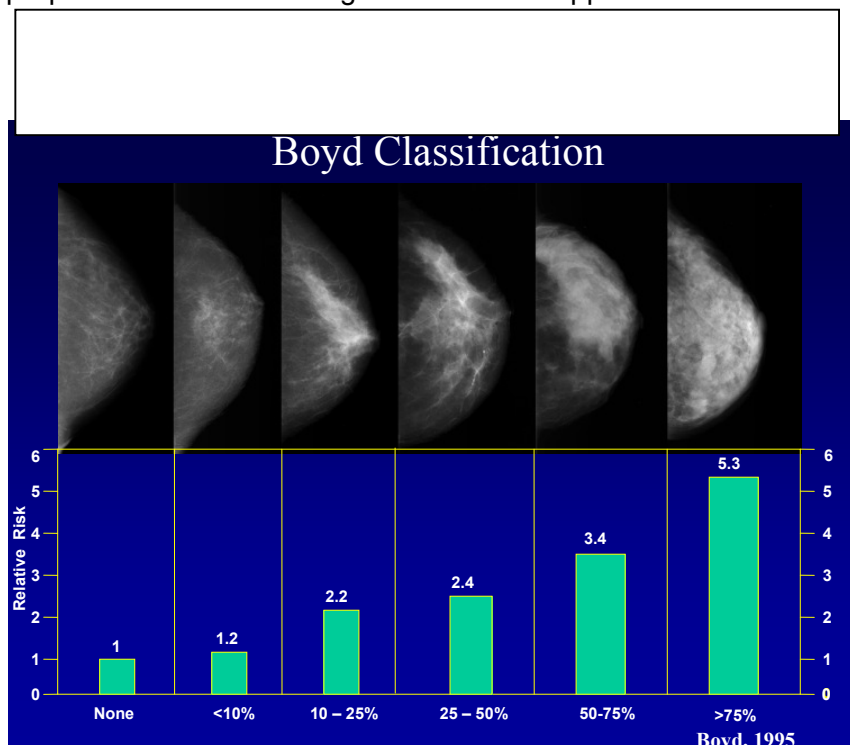
Women's Health Initiative study (WHI), the use of estrogen plus progestin was associated with a 74% increase in the risk of benign proliferative breast disease [hazard ratio, 1.74; 95% confidence interval (CI), 1.35-2.25](15). The anti-estrogen, tamoxifen, when used for breast cancer prevention, was associated with a 28 percent (RR 0.72, 95 percent Confidence Intervals 0.65-0.79) reduction in prevalence of benign breast lesions, including adenosis, cysts, duct ectasia, and hyperplasia (16).

Underlying and acquired genetic changes are also associated with benign breast lesions. Loss of heterozygosity (LOH), a finding caused by deletions of small segments of DNA (17;18) is commonly found in benign breast lesions. Women frequently have multi-focal lesions, each of which exhibit loss of heterozygosity (LOH) of differing regions of DNA. Women with BRCA1/2 mutations are found to have a high frequency of multiple benign or malignant breast lesions when bilateral mastectomy specimens are meticulously examined (19). These findings support the current theory of an underlying predisposition to mutations in some patients as the cause of multiple breast lesions (20). In the past, this phenomenon was termed a "field effect" and more recently, a "mutator phenotype" (20).

**Table 1.** Classification of Benign Breast Lesions on Histologic Examination, According to the Relative Risk of Breast Cancer.

| Risk | Proliferation | Histologic Findings |
|---|---|---|
| No increase | Minimal | Fibrocystic changes (within the normal range ): cysts and ductal ectasia (72%), mild hyperplasia (40%), nonsclerosing adenosis (22%), and periductal fibrosis (16%)*; simple fibroadenoma (15–23%)†; and miscellaneous (lobular hyperplasia, juvenile hypertrophy, and stromal hyperplasia) |
| | | Benign tumors: hamartoma, lipoma, phyllodes tumor,‡ solitary papilloma, neurofibroma, giant adenoma, and adenomyoepithelioma |
| | | Traumatic lesions: hematoma, fat necrosis, and lesions caused by penetration by a foreign body |
| | | Infections: granuloma and mastitis |
| | | Sarcoidosis |
| | | Metaplasia: squamous and apocrine |
| | | Diabetic mastopathy |
| Small increase (relative risk, 1.5–2.0) | Proliferative without atypia | Usual ductal hyperplasia, complex fibroadenoma (containing cysts >3 mm in diameter, sclerosing adenosis, epithelial calcifications, or papillary apocrine changes), papilloma or papillomatosis, radial scar, and blunt duct adenosis |
| Moderate increase (relative risk, >2.0) | Proliferative with atypia | Atypical ductal hyperplasia and atypical lobular hyperplasia |

## CLASSIFICATION OF PATHOLOGIC BENIGN BREAST LESIONS

A practical classification distinguishes lesions with no increase in breast cancer risk from those with a small (RR 1.5 to 2.0) or moderate (RR >2.0) increase in risk (Table I) (21). These risks have been validated by long term follow-up and the definition of specific lesions precisely defined by a consensus conference (21). An important basis of the classification is the degree of cellular proliferation (21;22). As described in a later section below, the relative risk with atypical hyperplasia increases to approximately 4 with follow up over more than 10 years.

## CLINICAL MANIFESTATIONS

Clinical presentations of benign breast disease are divided into those with pain, lumps, or breast discharge (Table 2).

**Breast Pain:** *Cyclic breast pain* usually occurs during the late luteal phase of the menstrual cycle, in association with the premenstrual syndrome or independently (23-28), and resolves at the onset of menses (23-24;26). A recent study in 1171 healthy American women indicated that 11% experience moderate to severe cyclic breast pain and 58%, mild discomfort (27). Breast pain interfered with usual sexual activity in 48% and with physical (37%), social (12%), and school (8%) activity in others. A role for caffeine, iodine deficiency, alterations in fatty acid levels in the

**Table 2.** Common Benign Breast Disorders in Women.

| Symptom or Finding | Possible Causes or Disorders |
|---|---|
| **Breast pain** | |
| Cyclic pain | Hormonal stimulation of normal breast lobules before menses |
| Noncyclic pain | Stretching of Cooper's ligaments<br>Pressure from brassiere<br>Fat necrosis from trauma<br>Hidradenitis suppurativa<br>Focal mastitis<br>Periductal mastitis<br>Cyst<br>Mondor's disease (sclerosing periphlebitis of breast veins) |
| **Nonbreast pain** | |
| Chest-wall pain | Tietze's syndrome (costochondritis)<br>Localized lateral chest-wall pain<br>Diffuse lateral chest-wall pain<br>Radicular pain from cervical arthritis |
| Non–chest-wall pain | Gallbladder disease<br>Ischemic heart disease |
| **Nipple discharge** | |
| Presence of galactorrhea | |
| From multiple ducts bilaterally | Hyperprolactinemia from pituitary tumor, hypothyroidism, drugs* |
| Absence of galactorrhea | |
| From one duct — elicited or spontaneous and bloody, with occult blood, or serosanguineous | Intraductal papilloma<br>Ductal carcinoma in situ<br>Paget's disease of breast |
| From multiple ducts — elicited and bloody or nonbloody, bilateral, black or clear | Fibrocystic changes<br>Ductal ectasia |
| **Discrete solitary lump** | |
| Age <30 yr | |
| Firm, rubbery lump | Most common lesion: fibroadenoma |
| Age 30–50 yr | |
| Firm, discrete lump | Most common lesions: fibroadenoma, cyst, fibrocystic changes, usual ductal hyperplasia, atypical ductal hyperplasia, atypical lobular hyperplasia† |
| Age >50 yr | |
| Firm, discrete lump | Most common lesions: cyst, ductal carcinoma in situ, invasive cancer |
| **Diffuse lumpiness ("lumpy-bumpy")** | |

breast, fat intake in the diet, and psychological factors in the etiology of breast pain remains unproven. *Non-cyclic breast pain* is unrelated to the menstrual cycle. Detection of focal tenderness is helpful diagnostically and suggests a tender cyst, rupture through the wall of an ectatic duct, or a particularly tender area of breast nodularity. Acute enlargement of cysts and periductal mastitis may cause severe, localized pain of sudden onset.

**Non-breast pain**: When arising from the chest wall, pain may be mistakenly attributed to the breast. Pain localized to a limited area and characterized as burning or knife like in nature suggests this possibility. Several distinct subtypes can be distinguished including localized or diffuse lateral chest wall pain, radicular pain from cervical arthritis and Tietze's syndrome or costochondritis. The method to distinguish between breast and non-breast pain by careful physical examination is illustrated on Figure 8 panels A-D.
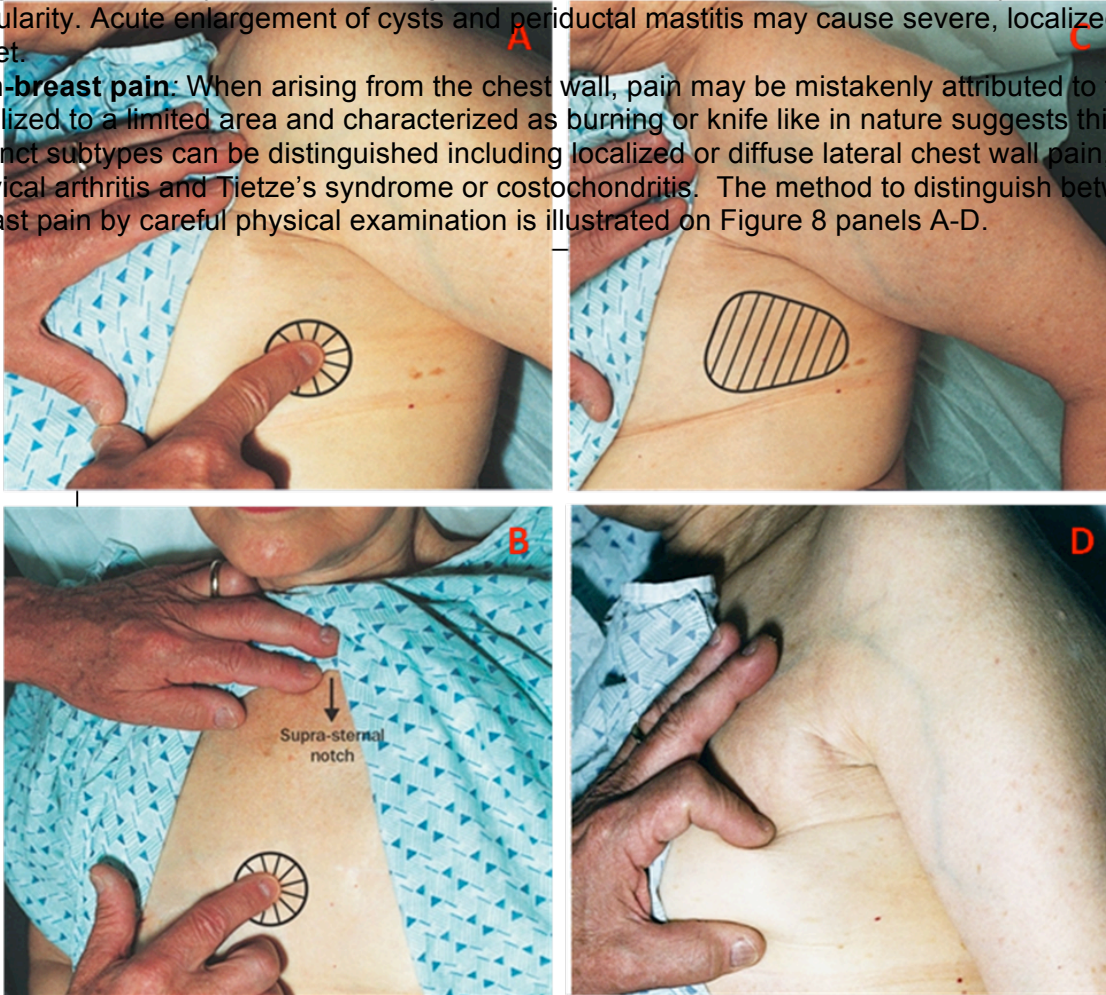


**Figure 8**. **A**. focal chest wall pain—lateral. The patient is turned 90º on her side so that breast tissue is no longer under the area of palpation. The index finger elicits a focal area of pain. **B**. Tietze syndrome. With the patient lying flat, the index finger elicits pain over a costochondral junction. **C**. diffuse lateral chest wall pain. With the patient turned over 90 degrees on her side, pain is elicited over a wider area of the chest wall. **D**. verification that squeezing breast tissue does not elicit pain ensures that the pain is not related to the breast but represents chest wall pain.

**Breast Nodules-** Proliferation of ductal or lobular tissue causes histologic changes that are manifested by the presence of palpable lumps or nodules. Patients often present with the finding of a new breast nodule on self-exam or are found to have a lump by their health care provider. Ninety percent of these new nodules in premenopausal women are benign and usually represent fibroadenomas in the early reproductive period (7). In the middle reproductive period, focal areas of fibrosis, hyperplasia, or cyst formation are more likely. In the later reproductive period, hyperplasia, cysts, and carcinoma in situ are more common. Some lesions present with symptoms suggesting the cause. With **duct ectasia**, penetration of the duct wall by lipid material may be

associated with a nodule exhibiting acute redness, and causing pain, and fever; after resolution, a subareolar nodule persists.

Other specific lesions present as lumps. These include multiple papillomas, sclerosing adenosis, and radial scars. **Multiple papillomas**—may present as breast lumps, nodules on ultrasound, or may be the cause of bloody nipple discharge and can be seen on ductography. **Sclerosing adenosis**—is a lobular lesion with increased fibrous tissue and interspersed glandular cells. It can present as a mass or a suspicious finding on mammograms. **Radial scars** are a pathologic diagnosis, usually diagnosed following mammography or palpation and then biopsy. Radial scars are characterized microscopically by a fibroelastic core with radiating ducts and lobules and impart a minimally increased risk of breast cancer similar to that of proliferative changes without atypia (29).

 **Nipple discharge:** 6.8 percent of referrals to physicians for breast concerns result from this symptom. Although particularly distressing to the patient, only 5 percent are found to have serious underlying pathology. Age is an important factor with respect to risk of malignancy (30). In one study, 3 percent for women younger than age 40, 10 percent between 40 to 60 and 32 percent > 60 with nipple discharge as their only symptom were found to have a malignancy.

A careful history characterizes breast discharge as either spontaneous or expressible. On examination, one can detect by careful inspection whether the discharge emanates from a single or multiple ducts. Nipple discharge can be divided into physiologic and pathologic types. Characteristics of physiologic discharge include non-spontaneous, multiple duct, bilateral, and non-bloody. Pathologic discharge is characterized as spontaneous, serous or bloody, usually unilateral and usually single duct. Reassuring characteristics are that it must be expressed; is green yellow, brown or milky; that it is bilateral and involves multiple ducts. Spontaneous discharge, whether serous or bloody, requires careful evaluation. A hemoccult card or urine dipstick can be used to test for occult blood if the discharge is spontaneous, unilateral, and from one duct. Milky discharge (galactorrhea) should be evaluated with measurement of a serum prolactin level. If the discharge is physiologic and the patient is under 35, only reassurance is necessary. Screening mammogram is recommended for patients over 35 with physiologic discharge. Pathologic discharge requires diagnostic mammogram, galactography (Figure 9) (30A), and referral to a surgeon.



Figure 9. Galactogram illustrating this. A catheter is inserted into the duct from which nipple discharge emerges. Contrast material is then injected through the catheter. The various branches of the duct are outlined.

The presence of crusting, scaling, and flaking of the nipple could be a manifestation of Paget's disease of breast and underlying cancer or of dermatologic problems. The approach is to obtain a history of other dermatologic problems, or a history of change in soap or clothing. If absent, a diagnostic mammogram should be obtained if the patient is over 35. In a large recent series of 1251 patients with nipple discharge, 433 had unilateral discharge and 194 had no breast lump in association with this symptom. Of these the lesions found included solitary papilloma (n=49), minimal breast cancer (n=20), fibrocystic disease (n=11), papillomatosis (n=7), lobular cancer (n=5) and duct ectasia (n=2)(30) (30,30A). For women with bloody discharge from a single duct, galactography is warranted. Filling defects can be due to intraductal papilloma, intraductal carcinoma, papillomatosis, debris, or air bubbles.

## APPROACH TO THE PRACTICAL MANAGEMENT OF BENIGN BREAST DISEASE

A detailed history and physical exam systematically evaluates the entire breast and chest wall and focuses on areas involving the patient's symptoms (Table 3). Diagnostic studies may then be ordered. For lumps, "The Triple Test" is recommended which includes palpation, imaging and percutaneous biopsy (either core or fine needle aspirate <FNA>). Mammography, often in conjunction with ultrasound examination (31-35) is required for evaluation of discrete palpable lesions in women over 35 whereas ultrasound provides an optional substitute in younger women. Round dense lesions on mammography often represent cysts which require only
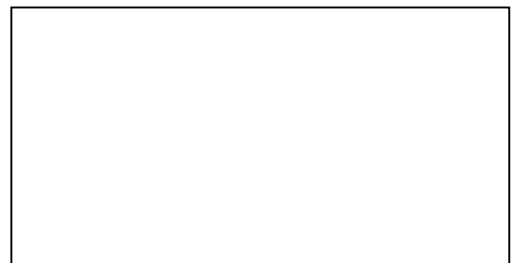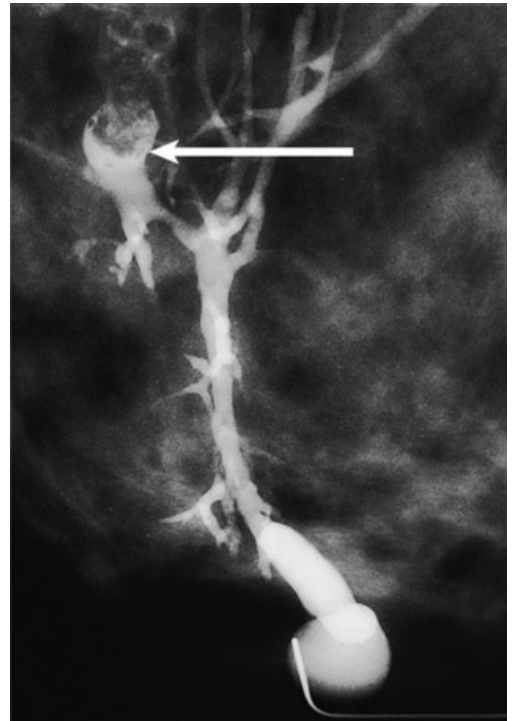
ultrasonography to distinguish them from solid lesions. Complex cysts containing both fluid and solid matter require biopsy.  For solid lesions, radiographically or ultrasonically directed core biopsy provides highly discriminative information regarding the presence or absence of malignancy. Core biopsy utilizes a large cutting needle deployed with a spring loaded, automated biopsy instrument and obtains tissue suitable for histologic analysis familiar to most pathologists. FNA frequently yields sufficient cellular material to allow adequate cytologic evaluation but requires an experienced cytopathologist. However, the amount of material obtained is insufficient to render a diagnosis in 35-47% of non-palpable lesions (36). The exact role of MRI in evaluating breast lesions is currently being determined (37). Galactography (ductography) is useful for detection of focal lesions in a single duct.  Cytology of nipple discharge is of limited value with the sensitivity of detecting malignancy only 35 to 47 percent (38).
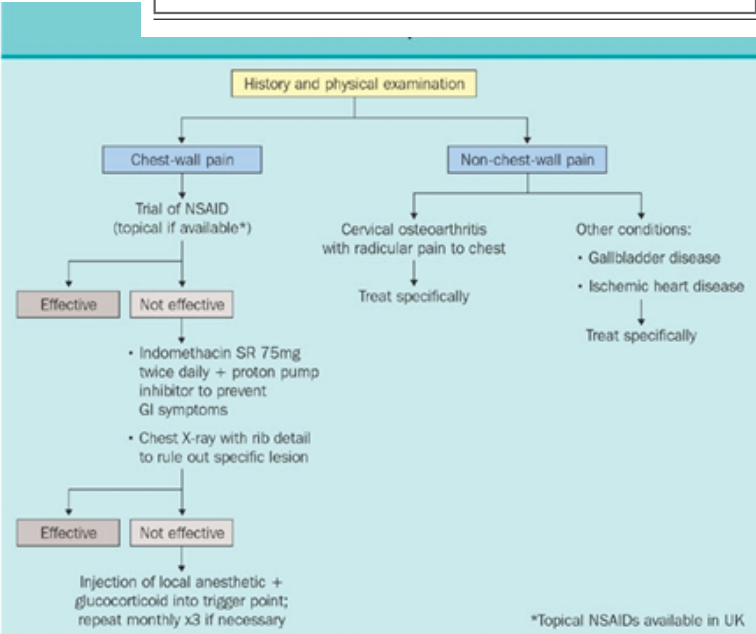
**Figure 10.** Evalu

### Diagnostic procedures

Ideally a team including a radiologist experienced in mammography, ultrasound, MRI and core needle biopsy as well as an internist, gynecologist, or surgeon with expertise in breast diseases should be involved in the evaluation of patients with breast disorders. An algorithm for evaluation and treatment of non-breast pain is shown below in figure 10. Information to be obtained by a focused history and physical examination are outlined on Table 3. The method of documenting whether breast pain is cyclic or non-cyclic is illustrated on Figure 8 A-D.  Imaging has become an integral part of the management of benign breast disorders.



Table 3. Clinical Examination of a Patient with Benign Breast Disease.

**History**

Characterize symptoms

Identify risk factors for breast cancer
    Age
        At menarche
        At first live birth
    Number of relatives with breast cancer or ovarian cancer
        Age at diagnosis
    Number of previous breast biopsies
    Presence of atypical hyperplasia or lobular carcinoma in situ on previous
        breast biopsy
    Weight gain after menopause
    Waist-to-hip ratio
    Results of bone-density testing

If patient is postmenopausal
    Age at menopause
    Duration of use of estrogen or progestin therapy

**Physical examination**

Palpate the four breast quadrants while patient is sitting and lying down
    Identify discrete lumps and examine for regional nodes
    Determine whether consistency is doughy with vague nodularity — find-
        ings consistent with fibrocystic changes
    Determine whether a discrete lesion has distinctly marginated borders —
        a finding consistent with fibroadenoma

Examine overlying skin, areola, and axilla

Determine degree of symmetry (asymmetry suggests underlying disease)

Examine nipple and seek to elicit discharge
    Determine whether galactorrhea is present
    Determine whether discharge is from one duct or from multiple ducts
    Determine whether discharge is viscous, watery, serosanguineous, grossly
        bloody, clear, blue–black, or green
    Determine whether occult blood is present

Seek to elicit chest-wall pain
    Examine costochondral junctions (Tietze's syndrome)
    Examine lateral chest wall while patient is lying on her side (at 90 degrees),
        to move breast away from chest wall
    Compare pain elicited by squeezing breast tissue with pain elicited by pal-
        pation of chest wall

### Imaging studies

Mammography is useful for evaluation of palpable lesions, particularly in those over 35. Digital or tomosynthesis mammography is preferred because of its ability to penetrate through dense breast tissue which is commonly found in younger women.  Ultrasound is often used as initial evaluation of a palpable mass in women under age 35. If a simple cyst is present, no further evaluation is necessary (Figure 11). If not, mammography may also be necessary to fully evaluate the lump. If the mass has findings suggestive of a fibroadenoma by ultrasound and mammography, short term follow-up and re-imaging can be considered (usually performed in 6 months). Experts are divided as to the necessity to biopsy all fibroadenomas.  MRI is more sensitive than digital mammography but false positives are more common (37). Routine yearly MRI is now recommended for women whose lifetime risk of breast cancer is > 20%. As an illustration of its sensitivity, 3% of the contralateral breasts in women with diagnosed breast cancer are found to have a second lesion in the opposite breast when examined by MRI (37).

## Findings on imaging studies

Fibrocystic change typically presents on mammogram as round or oval, well defined masses that can be subsequently shown to represent cysts on ultrasound (Figure 1.1). Diffusely scattered calcifications may also be found on the mammogram. Consequently, the goal of mammographic evaluation is to provide reassurance to the patient and physician that the risk of neoplasia is low. Aspiration of cysts is usually necessary only in a those cases where the mass does not fulfill all criteria for a simple cyst or if the cyst is painful. Biopsy may be necessary to confirm the benign nature of calcifications, particularly if clustered, linear or variously shaped.

For round masses or round calcifications on a first mammogram, the risk of cancer is less than 2%, and repeat mammography in 6 months is recommended. These lesions are termed "probably benign" using the lexicon terminology required by the Mammography Quality Standards Act (in the USA). If the risk is believed to be greater, core biopsy is recommended. Stereotactically directed core biopsy is ideal for evaluation of calcifications and provides highly discriminative information regarding the presence or absence of malignancy. If this technique is not available, insertion of a wire into the lesion radiographically followed by surgical excision or mere removal of a palpable lesion is warranted.



Figure 1.1 Ultrasonographic evaluation represents a non-dense black area representing cyst fluid. The lower panel is the corresponding area of calcifications showing a density. With the combination of mammogram and ultrasound, the lesion can be shown to be a cyst.

## Clinical guidelines for evaluation of nodules and discharge

Careful examination distinguishes solitary, discrete, dominant, persistent masses from vague nodularity and thickening. Practice Guidelines of the Society of Surgical Oncology (39) recommend the following evaluation: In women less than age 35, all dominant discrete palpable lesions require referral to a surgeon. If vague nodularity, thickening or asymmetrical nodularity is present, the examination is repeated at midcycle after one or two menstrual cycles.  If the abnormality resolves, the patient is reassured and if not, referred to a surgeon. Breast imaging may be appropriate. In women > age 35 with a dominant mass, a diagnostic mammogram (and frequently a sonogram) (32-35) is obtained and the patient referred to a surgeon. With vague nodularity or thickening, one obtains a mammogram with repeat physical exam at mid-cycle 1 to 2 months later and refers to surgeon if the abnormality persists. Post-menopausal women are referred for surgical consultation after a mammogram.  For gross cysts (i.e. > 4 cm), the guidelines suggest needle aspiration with repeat imaging within six months. If the aspirated fluid does not contain blood, the fluid is discarded without further histologic analysis unless the cyst contains solid components (i.e. complex cyst). If the fluid contains blood or if the cyst is complex, the, fluid is sent for cytology and consultation from a surgeon requested.  With persistent refilling of the same cyst after aspiration, surgical consultation is warranted.

Usual practice requires "the triple test" with palpation, mammography (often in conjunction with ultrasonography) and biopsy in women over age 35 with dominant masses. When mammography is negative but a dominant mass is present, biopsy is required to rule out malignancy since lobular carcinoma may not be seen on mammograms.  In those younger, mammography may be omitted if ultrasound and biopsy yield definitive information. Many experts omit biopsy in younger women with lesions characteristic of fibroadenoma on ultrasound and elect to follow carefully with serial ultrasounds at six monthly intervals for two years and yearly thereafter.  Since careful studies have shown that a lesion appearing benign on mammography and ultrasound is benign >99 percent of the time, clinical judgment may allow follow-up without biopsy in experienced hands (32-35).However, other experienced surgeons disagree and believe that all fibroadenomas require diagnostic core biopsy or FNA and especially in BRCA mutation carriers in whom medullary cancer may be found.  Biopsy confirmation of fibroadenoma eliminates the need for serial ultrasounds.  For those with a diagnosis of ADH (Atypical Ductal Hyperplasia) on FNA or core biopsy, excisional biopsy is then required since more complete resection often changes the diagnosis to DCIS.
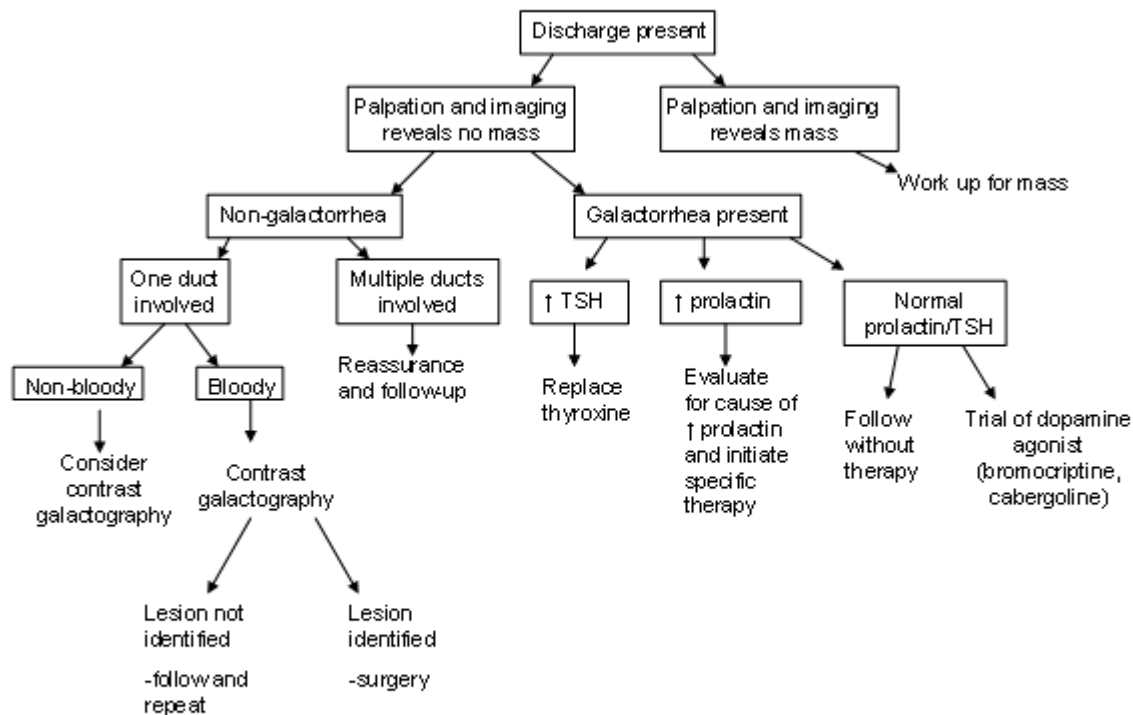
**Figure 12.** Treatment of Benign Breast Disease in Women
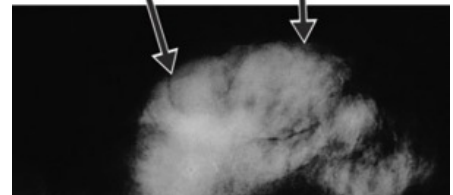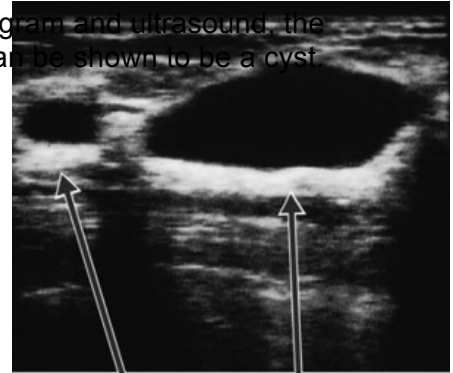
Breast discharge is evaluated according to the algorithm illustrated below on figure 12. Careful attention to several factors are necessary including determination whether the  discharge arises from one duct or multiple ducts, is bloody, or is milky.

### Algorithm for Evaluation of Nipple Discharge



Several well designed, randomized, controlled, double blind, cross over trials have validated the efficacy of medical therapy for **cyclic mastalgia**. Based upon these studies, we categorize therapies as definitely effective, definitely ineffective, possibly effective, and insufficiently studied. For classification as definitely effective, two or more randomized trials are required. For the category, possibly effective, one randomized trial must be positive in some respect but others may be negative. For the category definitely ineffective, prospective trials must be uniformly negative. For the category, insufficiently studied, only one randomized trial, either negative or positive is available.  For full details and references see Table 162-1 in Endocrinology, Fourth Edition, LJ DeGroot and JL Jameson, editors, WB Saunders Company, Philadelphia publishers; Chapter 162 Benign Breast Disorders, RJ Santen page 2194).

Danazol, bromocriptine, and tamoxifen have been proven to be effective (40-42, 43). Linoleic acid in the form of evening primrose oil has been shown effective in two randomized trials but not in the third, the largest trial. Its role in treatment therefore remains uncertain (44-46).  Vitamin E is considered *definitely ineffective* and iodine and vaginal progesterone *possibly effective*. Medroxyprogesterone acetate, caffeine avoidance, and progesterone have not been sufficiently studied.  Several other therapies have not been examined in randomized controlled trials but are likely to be beneficial since they are based upon physiologic principles. For example, precise fitting of a bra to provide support for pendulous breasts has been reported to relieve pain in observational studies.  GnRH agonist analogues are used to lower LH, FSH, and estradiol levels and to create a temporary post-menopausal state (47,48).  This therapy is reserved for patients in whom all other measures fail and the pain is considered severe. Reduction of the dosage of estrogens in post-menopausal women or addition of an androgen to estrogen replacement therapy (e.g. Covaryx[R],EEMT) appears to be beneficial in reducing breast pain (personal observations of author). Onset of menopause is known to reduce the frequency of breast pain.

*Relative efficacy of effective therapies*: No large randomized, controlled studies have compared the relative efficacy of danazol, bromocriptine, evening primrose oil and tamoxifen. Figure 13 rank orders them according to efficacy based upon data from individual reports from the same clinic. Minimal data are available from clinical trials which involve direct head to head comparisons. It should be noted that overall responses to danazol, bromocriptine and evening primrose oil are lower in those with non-cyclic pain than those with cyclic pain. However, not all studies have carefully excluded patients with non-breast pain and therefore conclusions regarding non-cyclic pain should be considered tentative.

**WOMEN AT HIGH RISK FOR BREAST CANCER**

A major consideration for women who present with breast problems is whether they have a higher than normal risk of developing breast cancer. Certain breast lesions such as **fibrocystic changes** are associated with increased risk of subsequent breast cancer (Table I). A 1.5 to 2-fold greater risk of development of breast cancer over a 20 year period of follow-up occurs with proliferative lesions including **ductal hyperplasia**, **lobular hyperplasia without atypia**, **sclerosing adenosis**, **diffuse papillomatosis** and **complex fibroadenomas.**

Figure 14: left panel —atypical lobular hyperplasia (ALH); right panel atypical ductal hyperplasia (ADH)

A recent report also suggested that radial scars increase relative risk by 1.8, a risk similar to that found in proliferative disease without atypia.

Recent follow-up data from a large, ongoing Mayo Clinic study data indicate that women with atypical hyperplasia–either lobular (ALH) or ductal (ADH) have a substantially increased risk of breast cancer in both the same and in the contralateral breast (49-50)(Figure 14). Over a mean period of 12.5 years, 698 women with either ADH (330) or ALH (327) or both (32) were followed and 143 or 20.4% developed breast cancer, either DCIS (19%) or invasive breast cancer (81%).

The average cumulative incidence of cancer increased steadily over a 25 year period (Figure 15). An important factor was the number of foci found. The incidence increased as the number of atypical foci increased reaching nearly 50% at 22 years for those with three or more foci (Figure 16).  When expressed as the relative risk of breast cancer, both ADH and ALH impart an approximately 4 fold increase in risk over time (Figure 17) and with 3 or more foci the risk increases to over 7 (Figure 18). The majority of the cancers diagnosed later were on the same side as the initial hyperplasic lesion and others were contralateral with the ratio of ipsilateral to contralateral at 2:1 for both ADH and ALH. However, there is a trend toward more contralateral tumors after a five year period and thereafter.It is interesting that the type of AH does not influence the type of breast
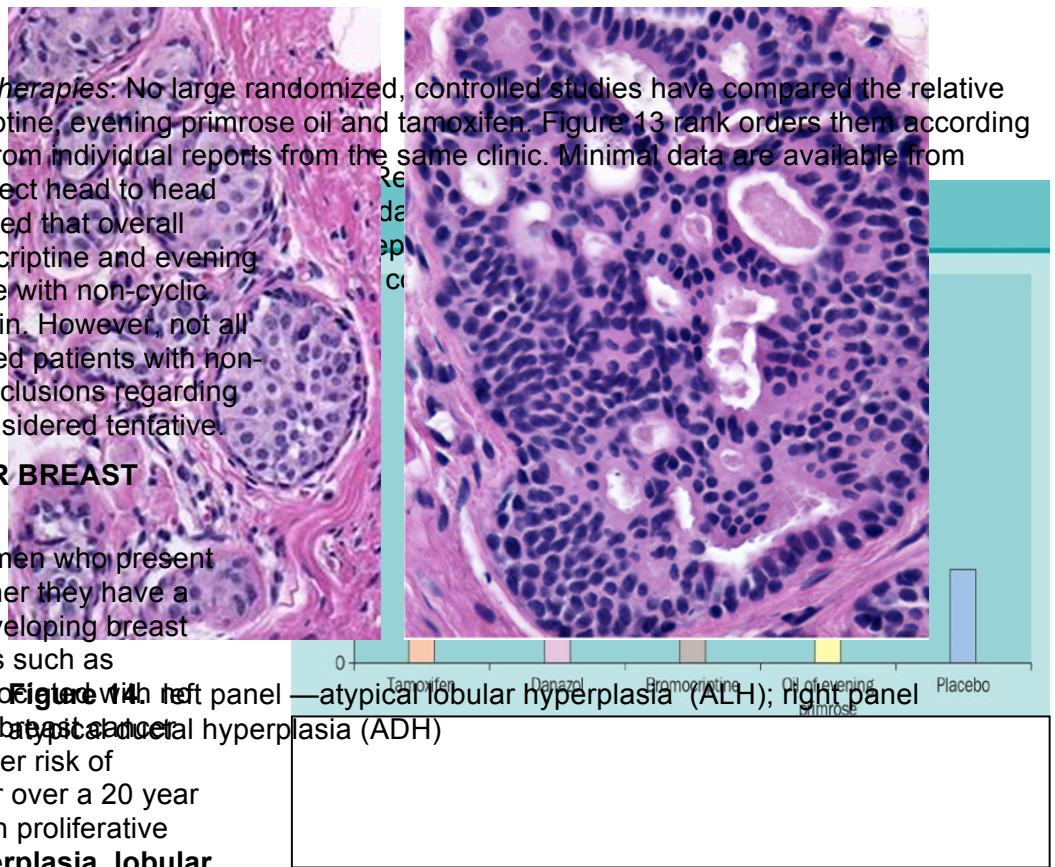
cancer that later develops. In women with ADH, 78% of later breast cancers were ductal and 23% lobular or other histologies. In comparison, in women with ALH, 77% of later cancers were ductal and 23% lobular or othe.

An area of substantial discussion over the years relates to the precise biology behind the increased risk. Since a lesion in one breast can impart an increased risk in the opposite breast, it would appear that these AH lesions reflect an underlying process in both breasts which at one time was called a field defect. More recent publications have substituted the term "mutator phenotype" for field defect to reflect the likelihood of an increased mutation rate in breasts with atypical hyperplasia lesions. Interpreting data on this basis, the contralateral lesions would be thought to reflect this mutator phenotype whereas the lesions in the ipsilateral breast might reflect a mother daughter relationship between the hyperplastic lesion and cancer. (Figure 19)

Lesions over-expressing HER-2/neu may also be associated with a higher risk of breast cancer in women (51). When the size of the area of atypia progresses even further, the lesions are no longer called benign but are classified as **carcinoma in situ.** The relative risk of development of invasive cancer when LCIS is present is increased 10 to 12-fold. While currently called lobular carcinoma in situ, this lesion is not generally considered to have reached the neoplastic stage but is analogous to atypical ductal hyperplasia. Nonetheless, the presence of LCIS warrants concern of a high risk of later developing invasive cancer in either breast.

Recent emphasis has been directed toward identification of molecular genetic markers which could predict which patients are at increased risk of developing breast cancer. In a recent study, presence of aberrant p53, p21, interleukin 6 and TNF alpha were associated with an increased in the relative risk of breast cancer (52). Another study of HER-2-neu reported a strong trend that this oncogene was also associated with an increased risk (51). Aneuploidy on flow cytometry has also been suggested as a marker of increased risk.

**Figure 16.** Cumulative incidence of breast cancer after diagnosis of atypical hyperplasia as a function of the number of foci found.
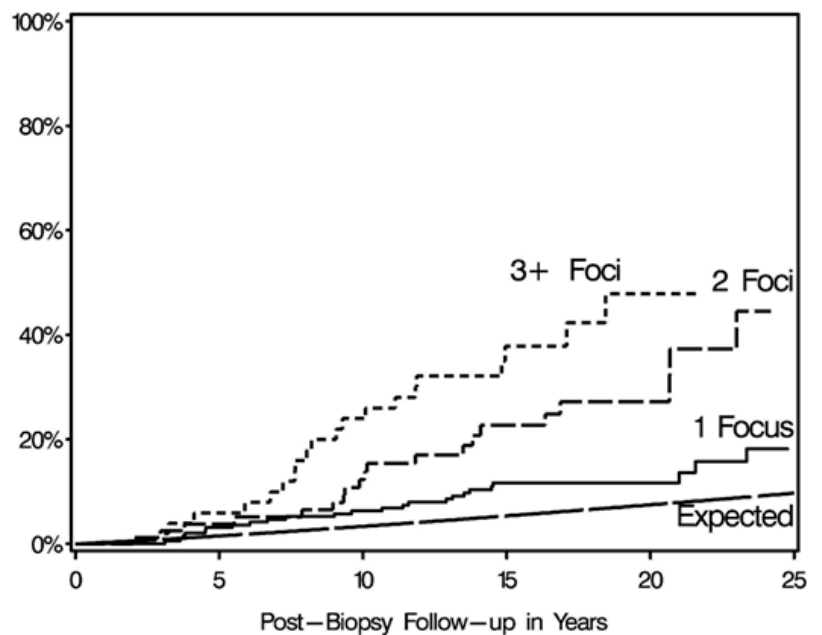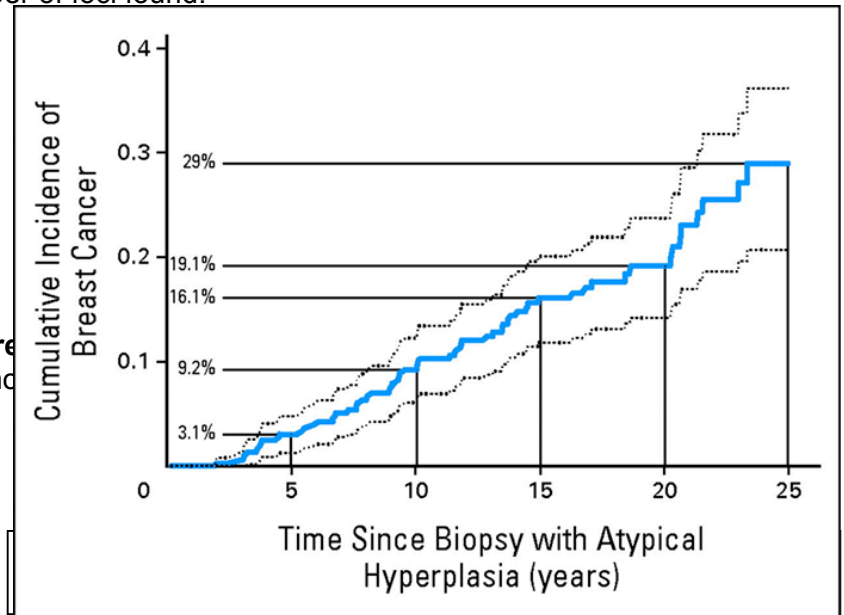




The presence of dense breast tissue on mammography has also been reported to be a predictor of increased incidence of breast cancer (figure 7). Ranked according to the categories of density, the increase in breast cancer risk from lowest to highest breast density has been reported to be as high as five fold. Two components of this finding must be considered**: one**, the presence of high breast density makes it more difficult to read mammograms and masks the sensitivity of finding a breast cancer initially but identifies it later and **two**, there is an increased risk of breast cancer associated with increased breast density. With long term follow-up studies, masking is not the explanation for the increased breast cancer risk (53).

**Figure 17**: Relative risk of breast cancer overtime after diagnosis of atypical hperplasia

**Figure 18**. Relative risk of breast cancer over time after diagnosis of atypical hyperplasia based

According to classic twin studies, heritability accounts for approximately 60% of the variation in breast density (54,55).  Breast cancer risk is also increased in association with high plasma estradiol and testosterone levels in postmenopausal women (53,56), and 20 kg or more weight gain (57) in the pre-menopausal years.
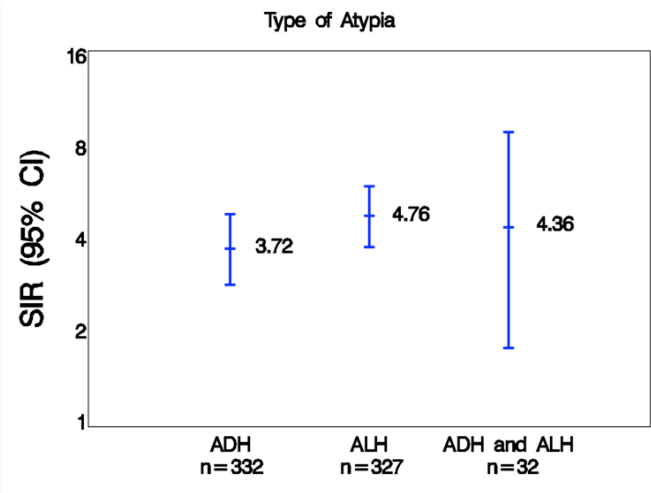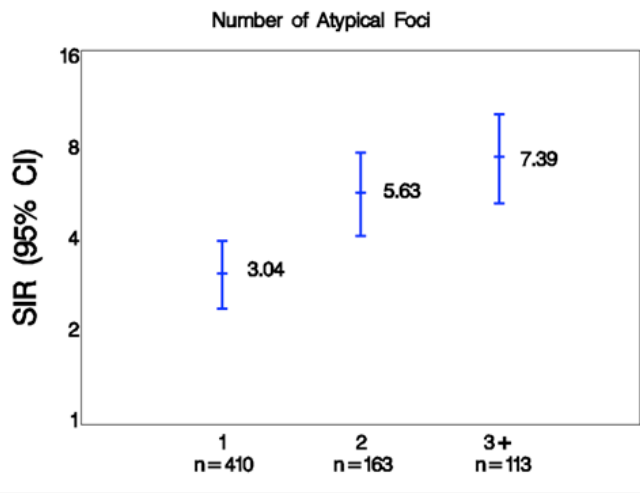


Type of Atypia

| | ADH n=332 | ALH n=327 | ADH and ALH n=32 |
| --- | --- | --- | --- |
| SIR (95% CI) | 3.72 | 4.76 | 4.36 |



Number of Atypical Foci

| | 1 n=410 | 2 n=163 | 3+ n=113 |
| --- | --- | --- | --- |
| SIR (95% CI) | 3.04 | 5.63 | 7.39 |

**Figure 19**. Comparison of ipsilateral versus contralateral breast cancers over time after a diagnosis of ADH or ALH. The tumors which occur contralaterally cannot be "daughter lesions'and likely reflect the propensity for lesion development on the contralateral side. This propensity has been called in the past a "field" defect and more recently a "mutator
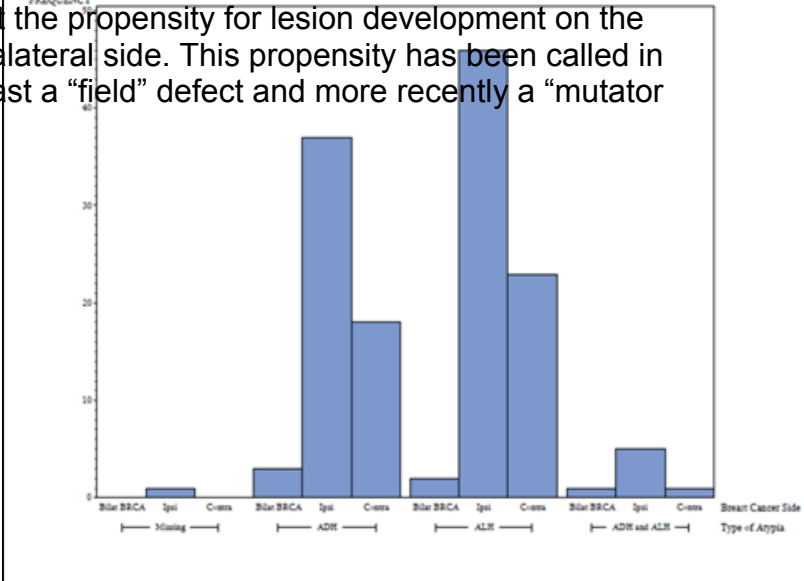


Another risk factor is use of hormone replacement therapy.  Current data from the Women's Health Initiative suggest a 26% increase in relative risk of breast cancer with conjugated equine estrogen (CEE) when combined with medroxyprogesterone acetate when used for an average of 7.1 years (58). This risk is probably increased further in women starting this therapy shortly after the menopause (i.e. a short gap between onset of menopause and start of menopausal hormone therapy) (59). Starting this therapy a long time after experiencing menopause (long gap) is associated with a lesser relative risk (59). The use of estrogen alone in the WHI was associated with a trend toward reduction of risk of breast cancer and a statistically significant reduction in those adhering to therapy (59).

The 11 year follow-up of the use of CEE alone demonstrated a statistically significant reduction in breast cancer risk (59A) .Use of CEE in short gap patients may be associated with some risk if used for more than five years but this has not yet been verified by randomized controlled trials. Available data suggest that the effects of menopausal hormone therapy in the WHI are a class effect and not related to the specific type of estrogen or progestin. One study, however, suggests that use of crystalline progesterone as the progestogen is assocated with a lesser risk than use of medroxyprogesterone acetate (60).

To aid in assessing breast cancer risk, a questionnaire developed by Gail, utilizes answers to 7 questions to calculate the 5 year and lifetime risk of developing breast cancer (61) This model has recognized deficiencies in that it does not consider second degree relatives with breast cancer, proliferative lesions of breast other than AH, alcohol intake, obesity, or birth control pill and menopausal hormone therapy (MHT) use. Nonetheless, the Gail model has been prospectively validated in over 6000 women followed for an average of 4.5 years. A more recently developed model, the Tyrer–Cuzick model (62) incorporates second degree relatives, obesity and use of MHT into its risk calculations. This model has been shown to be superior to the Gail model in one prospective study but further validation is necessary before general acceptance.

## BREAST CANCER PREVENTION

Patients with benign breast lesions imparting an increased risk of breast cancer can be offered tamoxifen (or raloxifene) as a prevention strategy. The risk of breast cancer is determined using the Gail model (or in women with a family history including second degree maternal or paternal relatives, the Claus or Tyrer-Cuzick models) and the benefits versus risks of tamoxifen evaluated. Risk factors not included in the Gail or Claus models include degree of breast density, plasma free estradiol levels, bone density, weight gain after menopause, and waist-hip ratio (13,56,57,63). Current recommendations suggest that women with a five year risk of breast cancer of over 1.67 percent and no contraindications to tamoxifen should be informed about the possibility of taking tamoxifen for five years (64,65,66,67). A recent overview has shown a 50 percent reduction of the relative risk of breast cancer with tamoxifen but benefits may be offset by increased risks of thromboembolic phenomena, endometrial cancer, and maturation of cataracts (68). The Star trial addressed whether raloxifene might be preferable to tamoxifen (69) and demonstrated relative equivalence. However, of interest was the fact that tamoxifen prevented more non-invasive breast cancers than did raloxifene (69). A longer term follow-up also reported a lesser reduction in breast cancer risk with raloxifene when compared to tomoxifen. Two trials, the MAP 17 and the IBIS II trial have now shown that aromatase inhibitors reduce the risk of breast cancer by 50-60% (70-71).

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