Benign Breast Disease and Cancer

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The term fibrocystic disease has become a catch-all for a variety of histologic and pathologic conditions, of which most have no prognostic significance. The vagueness of this entity is demonstrated by the many descriptions used to define it, some of which are listed in Table 1. Rather than perpetuate an erroneous concept or invent new synonyms for a process that has protean manifestations, it would be desirable to use a practical taxonomy in which the diagnosis of benign breast conditions is based on specific histologic criteria, with reasonably clear prognostic and therapeutic implications.

Anatomy and Physiology of the Breast

Knowledge of the anatomy and physiology of the breast is necessary for an understanding of the changes that fall into the category of benign breast disease. Glandular tissue forms 15–20 lobes, arranged radially about the nipple. Each lobe has its own excretory duct and is separated from the others by layers of fat and fibrous connective tissue, which run vertically through the breast, attaching the deep layer of subcutaneous fascia to the skin. This fibrous stroma forms suspensory bands known as Cooper’s ligaments. The lobes consist of multiple lobules connected by areolar tissue, blood vessels, and ducts, and the lobules, in turn, are composed of clusters of alveoli opening into numerous lactiferous ducts. These small ducts unite to form larger ducts and, eventually, a single canal, or tubule, for each lobe. They converge toward ampullae, dilations close to the nipple, which serve as reservoirs. Each tubule has a separate opening in the nipple. The main channels near the nipple are lined by a layer of flattened epithelium that first becomes cuboidal in the central area and then columnar in the small ducts in the periphery. The basal layer is composed of myoepithelial cells, circumferentially continuous around the ducts. These cells are spindle shaped and oriented in the long axis of the duct. Peripherally, the ductal cells, probably including the myoepithelial cells, have a secretory capacity. The alveoli are lined by a single layer of epithelium and a layer of myoepithelial cells resting upon the basement membrane. They resemble the structure of the peripheral ducts and often merge with them.

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TABLE 1. Terms for Benign Breast Disease

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<thead>
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<tr>
<td>Fibrocystic disease</td>
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<tr>
<td>Chronic cystic mastitis</td>
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<tr>
<td>Adenofibrosis</td>
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<tr>
<td>Fibrous mastopathy</td>
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<tr>
<td>Cystic mastosis</td>
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<tr>
<td>Cystic mastalgia</td>
</tr>
<tr>
<td>Mammary dystrophy</td>
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<tr>
<td>Fibroadenomatosis</td>
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<tr>
<td>Reclus’ disease</td>
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<td>Schimmelbusch’s disease</td>
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Estrogens promote ductal growth, and estrogens and progesterone together promote lobuloalveolar development. Pro-lactin and growth hormone are also important in the growth and function of the breast, possibly by augmenting the action of estrogen and progesterone and regulating the response of the breast to these hormones. Adrenal steroids, thyroid, insulin, and parathyroid hormones play a role in mammary function, either directly or in synergism with other hormones. As might be expected, cyclic increases in the quantity of glandular tissue are thus assured, and there is a concomitant vascular engorgement and enlargement of ductal lumina, which contribute to the swelling and discomfort many women experience in the luteal phase of their cycles, especially just premenstrually. During pregnancy, when the total volume of the breast greatly increases, these changes are even more exaggerated. Because all of the anatomic structures in the breast have estrogen and progesterone receptors and are subject to the ebb and flow of the hormonal tide, it is natural that they should undergo proliferation on a scheduled basis and that, as a result of variations in hormonal activity or in receptor content, one tissue or the other might undergo proliferation beyond the usual range. In many instances, this process is probably reversible. Biopsy specimens taken of women's breasts at various times in their cycles, therefore, may be expected to show a spectrum of proliferative changes, beginning with a moderate increase in epithelial activity and minimal dilations of the terminal lactiferous ducts. Larger cystic dilations may occur without any proliferation at all, giving rise to palpable masses and the misnomer, fibrocystic disease. In postmenopausal women the condition becomes static, but the anatomic changes that have occurred may persist. Although deficiencies in progesterone production and hyperestrinism have been incriminated and provide the basis for hormonal therapy, no consistent abnormality in the metabolism of estrogen, progesterone, androgen, or gonadotrophin has been proved to cause the development of benign breast disease.

Benign Breast Disease

Microcystic changes, those smaller than 2 mm in diameter, occur in 60–90% of women. Cysts larger than 2 mm in diameter occur in up to 20%. The cause of these cysts is obscure, and many explanations have been offered. There is the possibility of lobular duct obstruction, as the lumen becomes filled with cores of epithelial debris, or there may be an overgrowth of connective tissue surrounding the ducts, as a result of either secondary inflammation or increased estrogen stimulation, the end result being fibrosis and constriction. Only a small proportion of women with palpable cystic changes have symptoms other than the presence of lumpiness. The cysts may be accompanied by varying degrees of epithelial hyperplasia, which, with regard to the future development of cancer, is the most significant aspect of the process. Some cysts contain inspissated milk and are known as galactoceles.

Sclerosing Adenosis

Included in the category of benign breast disease are many other conditions, which may or may not be associated with the presence of cysts. These include sclerosing adenosis, an overgrowth of the lobular columnar and myoepithelium, associated
with a marked increase in the stromal connective tissue. Although highly proliferative, it is frequently a nonpalpable condition, and it occurs as an incidental finding in many biopsy specimens. Pathologists use the word "florid" to characterize extensive infiltration with loss of the normal lobular configuration, and, under these circumstances, sclerosing adenosis may easily be confused with cancer when examined under the microscope. The acinar cells maintain a benign appearance, however, and careful observation will avert misdiagnosis. Calcifications frequently are present, and these, combined with the dense mass of fibrous tissue that may develop in time, also may be confusing to the mammographer and the clinician.

**Fibroadenomas**

Fibroadenomas are an overgrowth of periductal stromal connective tissue, compressing entrapped ducts into a well-circumscribed and encapsulated lump. They are basically nonproliferative and benign but may grow to a very large size, especially in adolescents, occasionally encompassing most of the breast. They are not only easily palpable but have a characteristic appearance in mammograms. Very rarely the stroma develops a histologic pattern known as cystosarcoma phyllodes, a proliferative lesion that has been known to develop malignant tendencies in a few cases.

**Ductal Papillomatosis**

Ductal papillomatosis occurs in the peripheral duct system in the third and fourth decades of life and is not palpable. The epithelium is proliferative and may have atypical features that suggest carcinoma. Larger papillomas more often grow nearer the nipple and are usually single, producing a brown or bloody discharge. Because they are soft and friable they are often not palpable. Discharges containing red blood cells must be surgically investigated, even in the absence of positive clinical or mammographic findings.

**Duct Ectasia**

Duct ectasia is a poorly understood condition, consisting of multiple dilated ducts near the nipple containing inspissated secretions and surrounded by fibrous connective tissue. There is a chronic inflammatory reaction around the ducts, possibly due to the leakage of secretions into the adjacent tissues. This condition occurs in perimenopausal women and often in associated with a sticky, yellowish discharge. It can cause noticeable lumpiness in the breast but may undergo spontaneous regression.

**Benign Breast Disease and Cancer**

With the exception of fibroadenoma, the conditions noted above have not infrequently been found in the same breast with carcinoma, leading to the assumption that there is a cause and effect relationship. In studies of biopsy specimens, so-called fibrocystic disease has been found as often in noncancerous as in cancerous breasts. Retrospective studies designed to determine the incidence of fibrocystic disease in previous biopsy specimens of patients with cancer and of those without cancer have shown that there is no significant difference between the two groups. Prospective studies have been confusing because of many confounding variables and different types of controls. They suggest that patients followed after having had a biopsy specimen showing benign cystic disease have a twofold increased risk of having carcinoma develop, but these patients originally may have been in a high-risk category, or increased surveillance may have produced a higher detection rate. It is also possible that the original biopsy specimens were misinterpreted and that a more advanced process, such as lobular carcinoma in situ, was present at that time. Both lob-
ular carcinoma in situ and marked atypical epithelial hyperplasia are followed by a higher incidence of carcinoma when compared with matched controls.\textsuperscript{8,9}

If there is a connection between benign breast disease and carcinoma, it must reside in the cells of the epithelium, where the original in situ changes might be expected to occur. Increase of cancer risk seems to be based on the presence of atypical epithelial hyperplasia rather than cystic changes per se. Dupont and Page\textsuperscript{10} have proposed a taxonomy that is depicted in Table 2. Seventy percent of their patients had nonproliferative changes in their biopsy specimens, while 26% showed proliferation and were thought to be at slightly increased risk for the development of cancer. Only 4% had atypical epithelial hyperplasia, and they were calculated to be at a five times greater risk than the average person. Other factors, including family history of breast cancer and age, were also influential in determining the risk in this group.

A link between benign breast disease and cancer also has been sought in the levels of available estrogen receptors present in each, but the data to date do not support this concept. Nonmalignant lesions apparently less frequently have estrogen receptors and contain, on average, quantitatively less receptor than malignancies.\textsuperscript{11,12}

### Detecting Cancer

**Self-examination**

Because most conditions included under the general heading of benign breast disease cannot be proved to predispose to cancer, what can be done to reduce the likelihood that a woman will die of that disease? Periodic self-examination\textsuperscript{13,14} by motivated women is important in assessing changes in breast tissue that persist beyond the length of a regular menstrual cycle, and physicians are obligated to instruct patients in the proper way to perform the examination. The nodularity and soreness that many women note premenstrually may be confused with cancer, but the benefit of early diagnosis predominates over the anxiety engendered by misinterpretation.

**Examination by a Physician**

Beginning at age 25, patients at risk for the development of breast cancer should have regular breast examinations by a physician, or knowledgeable surrogate, and all women should have thorough breast examinations at the time of their periodic health check-ups. Very dense breasts make examinations difficult and relatively inaccurate, because, under those conditions, lumps smaller than 1 cm may be impossible to palpate. Epithelial hyperplasia, which is a risk factor, is nonpalpable unless major proliferation has occurred. Ductal papillomas and sclerosing adenosis are often nonpalpable, and lobular carcinoma in situ also may be occult. Diagnostic aids must be used adjunctively to balance the inaccuracies inherent in physical examination and to detect lesions that are not palpable or are in a transitional stage in the development of cancer.

**Mammography**

Mammography with its variants, including xeroradiography, magnification mammography, and computerized tomography, has proved itself as a screening technique.\textsuperscript{15,16}
With a false-negative rate of less than 10% for this method, qualified interpreters can discern abnormalities unrecognizable clinically. The dosage rate of less than 0.5 rads incurred by patients in first-class institutions permits multiple examinations without undue exposure and undue risk of radiation-induced cancer. The benefit of x-ray examination related to risk is 47:1 in women older than 40 whose mothers had cancer and 4:1 to 8:1 in asymptomatic women between 40 and 49 who don’t have a family history of cancer. As in the case of physical examination, accuracy of diagnosis is hindered by dense breasts, but to a lesser degree. Ideally, the technique should be applied to mass populations within the guidelines set by the American Cancer Society in 1983. These call for a screening baseline mammogram for patients between the ages of 35 and 40, followed by annual or biannual mammograms from ages 40 to 49, and annual mammograms after age 50. The enormous cost of such an operation has imposed a certain degree of selectivity, but this cost must be weighed against the benefit of greater salvage and resulting savings on the long-term treatment of advanced cancer.

In an effort to extend the usefulness of the procedure to include the diagnosis of possible precancerous disease, mammographers have become more aggressive. Terms such as dystrophy and dysplasia, the former suggesting the “morbid growth of cancer” and the latter having a histologic connotation, are employed, even though only shadows are being described. Some disagreement exists, but such parenchymal patterns in x-rays have not been highly successful in helping to select asymptomatic women who might be at high risk for malignant disease. Although semantically incorrect, the radiologic terminology is now embedded in the literature and must serve as a warning to the clinician, even if it cannot always be taken literally. Consultation with the radiologist for clarification is indicated. The reported prevalence of cancers in dense breasts may be due to the fact that they are more difficult to detect by any method and are consequently at a more advanced stage when detected. Reports of mammograms sometimes contain elaborate descriptions and, occasionally, instructions to the physician, which usually must be heeded for the physician’s as well as the patient’s sake. Biopsies must be done as ordered unless the lesion noted has been sampled previously. Commands to repeat the study in 3, 6, or 9 months should be followed by a consultation with the mammographer to determine the rationale, and subsequent action should depend upon combined judgment.

**Additional Methods of Detection**

The search for a less expensive and less invasive modality than mammography led to the further development and reappraisal of several old techniques and the discovery of some new ones. Beyond traditional telethermography, with which thermal patterns in the breast are detected by sensors held above it, a more refined technique, graphic stress telethermography, has evolved. Cooling the patient’s hands before testing, to increase the differential between normal areas and hot spots, and using infrared sensors of high resolution along with computerized mapping have been reported to identify high-risk women. Another relatively recent variant, liquid crystal thermography, consists of pressing the breasts directly against a plate in which cholesteric crystals are suspended. The crystals change color in response to temperature change, and the image can be viewed directly, as well as recorded. Differences in skin temperature are demonstrated. In spite of these advances, the false-positive rate for thermography remains high, tending to cause an unacceptable increase in the number of biopsy specimens with normal results. In
its current state, its ability to diagnose early disease is questionable.

Transillumination of the breast and mapping of its anatomy by fiberoptic light is known as diaphonography. This method has been publized in the lay press, but no data support the claim that it can demonstrate invasive disease that is not already obvious or that it can screen for early disease.

Ultrasonography can distinguish between solid and cystic masses, but it has not proved its efficiency as a screening tool or in diagnosing early lesions. None of these techniques has been subjected to rigorous prospective studies, and they must be considered inferior to mammography in this respect. The rush to market new equipment and establish successful breast diagnostic clinics has led to claims of accuracy that have not been scientifically substantiated. If they are widely used as substitutes for clinical evaluation and mammography, it is possible that the delay in the diagnosis of early cancer may lead to irreparable harm.

Computerized tomography of the breast has advantages similar to those of mammography but is far more expensive. In special situations it may add an extra dimension in the diagnosis of occult disease. Magnetic resonance imaging is being tested, but its full potential has not yet been demonstrated.

**Biopsy**

It is apparent that early breast cancer cannot be definitively differentiated from the various kinds of benign breast disease or even from normal breast tissue by physical diagnosis or by diagnostic aids, nor can biopsies be performed on all breasts. Criteria must be established to select patients for biopsy, an expensive and anxiety-provoking experience for the patient. The surgeon must exercise his or her best judgment when recommending this procedure. Lesions upon which biopsies will be performed include all discrete masses or lumps and all dominant projections from thickened areas noted, or previously described, in the breast. Surgical investigation is indicated for areas in which there has been a rapid increase in size of a previously noted thickening not related to changes in the menstrual cycle, nipple discharge not related to pregnancy or hormonal causes, unexplained erythema or edema, areas of skin or nipple retraction, and pseudoezematous changes in the overlying skin. Mammographic findings suggestive of malignancy always necessitate biopsy.

Open surgical biopsy under local anesthesia is the method of choice. In general, the incision should be circumareolar or, if necessary, parallel to the areolar margin further out in the breast, in order to provide the best cosmetic result. Small lesions and fibroadenomas are totally excised with a small margin of surrounding tissue, but larger lesions, the removal of which might seriously jeopardize the contour of the breast, are incised and a representative specimen taken. Incisions are made in a way that will not interfere with the subsequent removal of a sufficient margin of skin, should a mastectomy be necessary later. If a small carcinoma is encountered, it may be totally removed with a significant surrounding margin, but larger cancers are best sampled and left for later definitive therapy. Approximately 20% of breast biopsy specimens should show malignant disease; a lower ratio suggests that the surgeon is too liberal in his indications and a higher, that he or she is too conservative. Lumps that are thought to be cystic may be aspirated safely. The fluid is quite acellular and usually nondiagnostic, but it is best to send it to the laboratory for a pathologic opinion, even though it will be normal in nearly all cases. Aspiration of solid tumors, using a fine needle and making multiple passes through different
planes of the lesion, may be attempted.\textsuperscript{36,37} The material thus obtained is sent to cytol-
ylogy, and a reasonably accurate diagnosis can be made by expert pathologists, but it is
dangerous to base a decision for definite therapy on a positive cytologic report. Negative
aspirations are invalid, and further evaluation is required. Tissue samples large enough for sections and histologic
appraisal can be obtained with a cutting needle, of which several excellent models are available. If these are positive, they may
be considered reliable.

Nonpalpable lesions, noted only on mammograms, must be localized for biopsy by the preoperative insertion of a
guide wire under x-ray visualization. After excision, the tissue is sent back to radiology for positive identification. Soft papillomas
are found by dissection of the main tubules, where the larger lesions are located, or removal of a representative block of
more peripheral tissue. The presence of a bloody discharge necessitates this type of
exploration.

\section*{Surgical Management}

Prophylactic subcutaneous mastectomy with insertion of a prosthesis either above or, preferably, below the pectoralis major
muscle has been advocated for dense breasts defying accurate diagnosis, for condi-
tions considered premalignant, and for patients with a background of multiple risk
factors.\textsuperscript{38,39} The operation carries its own risks and side effects, and the necessity to
preserve some tissue below the skin prevents it from being completely effective. It
may be considered for lesions thought to have a short lag time before the develop-
ment of cancer, such as lobular carcinoma in situ, and for women who have over-
whelming cancer phobia, but sound surgical judgment is required to assess the
indications and the risk benefit ratio. It is fascinating that mastectomies are being ad-
vocated for benign disease at a time when

some overt malignancies are treated by local excision followed by irradiation.

\section*{Treating Benign Breast Disease}

Many regimens have been proposed both for the prophylaxis and the therapy of ben-
ign breast disease. Oral contraceptives have been used to regulate the hormonal
milieu and, in some instances, have provided symptomatic relief, presumably by
regulating estrogen and progesterone produc-
tion. Whether oral contraceptives provide protection against the eventual de-
velopment of cancer remains unsettled, but the data in most epidemiologic studies of-
er assurance that they do not increase the
incidence of the disease, regardless of dosage, duration of use, age, or family
history.\textsuperscript{40–43} However, a broad spectrum of benign conditions has been included in
these studies, and there is no guarantee of the innocuous effect of oral contraceptives
on such specific entities as atypical epi-
thelial hyperplasia.

Estrogen therapy at and after the meno-
pause is now considered standard therapy
for the alleviation of vasomotor symptoms
and vaginal dryness, as well as prophylaxis against the development of osteoporosis,
but fear persists that exogenous estrogens
may be cancerogenic, especially to those in
a high-risk category. Although estrogen is
known to stimulate growth of preexisting

cancer, there are no good data showing a
direct causative effect on the initial stages
of the disease, either in patients with nor-
mal breasts or in those thought to have
benign breast disease.\textsuperscript{44} Paradoxically, es-

trogen is known to promote regression of
recurrent breast cancer in some post-
menopausal women.\textsuperscript{45} A study showing the
protective effect of progesterone, when
added to an exogenous estrogen regimen
for postmenopausal women\textsuperscript{46,47} has re-
ceived much attention, but further confir-
mation of this alleged advantage is needed.
It has been known for years that androgenic drugs inhibit the growth of breast tissue, and testosteronelike drugs have been administered to patients with malignancy and with benign breast disease, with some improvement in both instances. In recent years, an impeded androgen, Danazol, having fewer virilizing side effects, has been used to alleviate the symptoms of benign breast disease. This drug has proved helpful in relieving symptoms, and the effect has been shown to last beyond the period of usage.38 No data are available to indicate that Danazol protects against the future development of cancer.

During the past 20 years dietary intervention has been recommended for the control of symptoms thought to be due to benign breast disease and for the prevention of cancer. Clinical trials of vitamin E supplements have been reported to show relief of symptoms in a significant number of treated women as compared with controls.49 These reports have not been confirmed by rigidly controlled trials,50 nor has an adequate rationale been formulated as to the mechanism of action of vitamin E on the breast parenchyma or its supporting hormones.

Withdrawal of methylxanthines, a component of many favorite beverages including coffee, tea, cola, and cocoa, from the diets of women with cystic changes in the breast has been advocated to reduce the disease and alleviate the symptoms of mastalgia. Based on laboratory studies, which show high levels of cyclic adenosine monophosphate and guanosine monophosphate in the breast tissue of women with benign disease, it is hypothesized that the action of phosphodiesterase, an enzyme necessary for the metabolism of cyclic AMP and GMP, has been impeded by high circulating levels of the methylxanthines.51 Lowering these levels should enhance the action of the enzyme and permit cellular activity to proceed normally. The original clinical studies indicated that such was indeed the case, but large-scale well-controlled trials have failed to show significant improvement either in symptoms or pathologic anatomy.52–54 Diagnostic aids have been said to show objective evidence of changes in the breast tissue, and individual patients will attest to the efficacy of this dietary restriction, but credible objective evidence is lacking. As in the case of vitamin E supplements, the withdrawal of methylxanthines cannot be said to have other than a placebo effect on the relief of symptoms or reduction in the disease process. Certainly these methods have no long-range benefits.

Epidemiologic studies have clearly defined differences in the risk of breast cancer in various ethnic groups, the incidence being higher in western countries than in eastern, and in populations indulging in diets high in red meat.55 How important geographic and dietary factors may be in the etiology of cancer is still debatable, but a similar correlation has not been reported for cystic disease of the breast. Until accurate scientific information on the subject is forthcoming, moderation in the level of intake of meat and animal fat may be recommended.

References
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