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REVIEW

Breast Cancer: A Review of the Literature

Rodney C. Richie, MD, FACP, FCCP; John O. Swanson, MD

This article presents a comprehensive review of the Breast Cancer literature examining epidemiology, diagnosis, pathology, ''benign'' breast disease, breast carcinoma *in situ* syndromes, staging, and post-treatment surveillance among many topics. Breast cancer remains the most commonly occurring cancer in women. Breast cancer detection, treatment, and prevention are prominent issues in public health and medical practice. Background information on developments in these arenas is provided so that medical directors can continue to update their approach to the assessment of breast cancer risk.

Address: Texas Life Insurance Company, 900 Washington Avenue, Waco, TX 76701.

Correspondent: Rodney C. Richie, Medical Director, Texas Life Insurance Company.

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EPIDEMIOLOGY

Breast cancer is the most commonly occurring cancer in women, comprising almost one third of all malignancies in females. It is second only to lung cancer as a cause of cancer mortality, and it is the leading cause of death for American women between the ages of 40 and 55.[1] The lifetime risk of a woman developing invasive breast cancer is 12.6 % – one out of 8 females in the United States will develop breast cancer at some point in her life.[2]

The death rate for breast cancer has been slowly declining over the past decade, and the incidence has remained level since 1988 after increasing steadily for nearly 50 years.[3] Twenty-five percent to 30% of women with invasive breast cancer will die of their disease.[1] But this statistic, as grim as it is, also means that 70% to 75% of women with invasive breast cancer will die of something *other* than their breast cancer. Hence, a diagnosis of breast cancer, even invasive breast cancer, is not necessarily the ''sentence of death'' that many women (and their insurance companies) imagine.

Mortality rates are highest in the very young (less than age 35) and in the very old (greater than age 75).[4] It appears that the very young have more aggressive disease, and that the very old may not be treated aggressively or may have comorbid disease that increases breast cancer fatality.[5]

Although 60% to 80% of recurrences occur in the first 3 years, the chance of recurrence exists for up to 20 years.[6,7]

PATHOLOGY OF BREAST CANCER

Ninety-five percent of breast cancers are carcinomas, ie, they arise from breast epithelial elements. Breast cancers are divided into 2 major types, *in situ* carcinomas and invasive (or infiltrating) carcinomas. The in situ carcinomas may arise in either ductal or lobular epithelium, but remain confined there, with no invasion of the underlying basement mem-

Table 1. Chances of a Woman Developing Breast Cancer by Age

By Age	Normal Risk	Genetic Risk*
45	1 in 93 (1%)	42%
55	1 in 33 (3%)	72%
65	1 in 17 (6%)	80%
75	1 in 11 (9%)	84%

* Breast-related cancer antigen 1 and 2 (BRCA-1, BRCA-2). Data from American Cancer Society, Cancer Facts and Figures 2000.

brane that would constitute extension beyond epithelial boundaries. As would be expected with such localized and confined malignancy, there is negligible potential for metastases.

When there is extension of the ductal or lobular malignancy beyond the basement membrane that constitutes the epithelial border, then the malignancy is considered invasive (or infiltrating) ductal or lobular carcinoma. The potential for metastases and ultimately death occurs in invasive disease.

RISK FACTORS FOR DEVELOPMENT OF BREAST CANCER

Breast cancer incidence is highest in North America and Northern Europe and lowest in Asia and Africa. Studies of migration patterns to the United States suggest that genetic factors alone do not account for the incidence variation among countries, as the incidence rates of second-, third- and fourth-generation Asian immigrants increase steadily in this country. Thus, environmental and/or lifestyle factors appear to be important determinants of breast cancer risk.[5]

Gender is by far the greatest risk factor. Breast cancer occurs 100 times more frequently in women than men. In women, incidence rates of breast cancer rise sharply with age (see Table 1) until ages 45 to 50, when the rise becomes less steep.[4] This change in slope probably reflects the impact of hormonal change (menopause) that occurs about this time. By ages 75 to 80, the curve actually flattens and then decreases.

Despite the steepness of the incidence curve at younger ages, the more important issue is the increasing prevalence of breast cancer with advancing age, and the take-home message for physicians and underwriters alike is that any breast mass in a postmenopausal woman should be considered cancer until proven otherwise.[8]

Genetics plays a limited but important role as a risk factor for breast cancer. Only 5% to 6% of breast cancers are considered hereditary.[9] BRCA-1 and BRCA-2 account for an estimated 80% of hereditary breast cancer, but again, this only represents 5% to 6% of all breast cancers. BRCA-1 and/or BRCA-2 positive women have a 50% to 85% lifetime risk of developing breast cancer (see Table 1), and a 15% to 65% risk of developing ovarian cancer, beginning at age 25.[10]

Familial breast cancer is considered a risk if a first-degree relative develops breast cancer before menopause, if it affected both breasts, or if it occurred in conjunction with ovarian cancer.[11] There is a 2-fold relative risk of breast cancer if a woman has a single first-degree relative (mother, sister or daughter). There is a 5-fold increased risk if 2 first-degree relatives have had breast cancer.[12]

A woman's hormonal history appears to be a risk factor, as the relative risk of breast cancer seems to be related to the breast's cumulative exposure to estrogen and progesterone. Early menarche (onset of menstruation $<$ age 13), having no children or having them after age 30, and menopause after age 50 and especially age 55—all these mean more menstrual cycles and thus greater hormone exposure.[13]

The Women's Health Initiative (WHI), a randomized controlled trial of 16,608 postmenopausal women comparing effects of estrogen plus progestin with placebo on chronic disease risk, confirmed that combined estrogen plus progestin use increases the risk of invasive breast cancer.[14] Hormone replacement therapy (HRT) users have a breast cancer risk that is 53% higher for combination therapy and 34% higher for estrogen alone, especially if used for more than 5 years. Al-

though earlier studies suggested that this increased risk of cancer was offset by the fact that the cancers induced by HRT were of more benign pathology and had a more favorable prognosis,[4] reevaluation of the WHI data reveals this impression to be incorrect. Invasive breast cancers associated with estrogen plus progestin use were larger (l.7 cm vs 1.5 cm, p = 0.04), were more likely to be node positive (26% vs 16%, p = 0.03), and were diagnosed at a significantly more advanced stage (regional/metastatic 25.4% vs 16%, p = 0.04). The percentages and distribution of invasive ductal, invasive lobular, mixed ductal, and lobular as well as tubular carcinomas were similar in the estrogen plus progestin group vs the placebo group.[15]

Over observation time as short as a year, there was a statistically significant increase in breast density in the estrogen plus progestin group, resulting in increased incidence of abnormal mammograms (9.4% vs 5.4%, $p<0.001$).[15] As noted by Gann and Morrow in a *JAMA* editorial, ''the ability of combined hormone therapy to decrease mammographic sensitivity creates an almost unique situation in which an agent increases the risk of developing a disease while simultaneously delaying its detection.''[16]

Li et al reported that women using unopposed estrogen replacement therapy (ERT) had no appreciable increase in the risk of breast cancer. However, use of combined estrogen and progestin hormone replacement therapy had an overall 1.7-fold (95% CI 1.3–2.2) increased risk of breast cancer, including a 2.7-fold (95% CI 1.7–4.3) increased risk of invasive lobular carcinoma, a 1.5-fold (95% CI, 1.1–2.0) increased risk of invasive ductal carcinoma, and a 2-fold (95% CI 1.5–2.7) increased risk of ER+/PR+ breast cancers.[17]

Other risk factors for breast cancer include alcohol, which has been linked to increased blood levels of estrogen interfering with folate metabolism that protects against tumor growth. Women who drink >2 ounces of alcohol per day are 40% more likely to develop breast cancer than women who drink no alcohol.[18]

The Nurses' Health Study found that in postmenopausal women a weight gain of more than 45 pounds after age 18 was linked as an independent risk factor for breast cancer (fat tissue produces hormones that are converted to estrogen).[19] This association was stronger in postmenopausal women who had never taken estrogen replacement therapy. The relative risk of developing breast cancer was 1.6 with a 10–20 kg weight gain, and 2.0 with a weight gain of more than 20 kg, compared to women with minimal weight gain. In contrast, among women taking estrogen, those who gained weight did not have an increased risk of breast cancer. The differing effects of obesity and weight gain in premenopausal and postmenopausal women is thought to be because obesity decreases estradiol and progesterone concentrations in premenopausal women because of an increased frequency of anovulation.[20] Thus, less circulating estrogen is available to target tissues such as the breast.

The Nurses' Health Study also found that postmenopausal women who got at least 1 hour of physical exercise *per week* were 15% to 20% less likely to develop breast cancer than those who were completely sedentary. In regularly exercising women, participants in a health-screening program in Norway, the reduction in risk was greater in premenopausal women than in postmenopausal women (relative risk 0.38; 95% CI 0.19–0.79).[21] The reason for the reduction of risk in exercising women may be related to delayed menarche in young girls involved in strenuous physical activity. Also, moderate levels of physical activity in premenopausal women are associated with anovulatory cycles, which also are associated with decreased risk.[22]

Women treated for breast cancer have about a 1% greater chance per year of developing a new second cancer in either the treated breast or the other breast. Therefore, previous breast cancer is an accepted risk factor for development of breast cancer.[23] Ten percent of women with breast cancer develop a second breast cancer, and women with breast cancer have a 3- to 7-fold increased relative

risk of cancer developing in the opposite breast.

Women who have had high doses of radiation to the chest before age 45—usually for Hodgkin's disease—are at significantly increased risk of breast cancer as adults. Radiation after age 45 does not confer increased risk. The most vulnerable ages appear to be the prepubertal years of 10 to 14. These women should have yearly mammograms and clinical breast exams beginning either 10 years after the radiation treatments or by age 35.[24]

RELATIONSHIP OF BENIGN BREAST DISEASE WITH BREAST CANCER

This is an issue of great concern for patients, physicians and insurance companies alike, as there are conditions that confer no risk of malignancy and others that definitely confer increased risk.

Breast biopsies conferring no significantly increased risk for malignancy include any lesion with non-proliferative change.[25,26] These include duct ectasia and simple fibroadenomas, benign solid tumors containing glandular as well as fibrous tissue. The latter is usually single but may be multiple. Solitary papillomas are also benign lesions conferring no increased risk of future malignancy, despite the fact that they are often (in 21 of 24 women in a single study[27]) with sanguineous or serosanguineous nipple discharge. Fibrocystic change (cysts and/or fibrous tissue without symptoms) or fibrocystic disease (fibrocystic changes occurring in conjunction with pain, nipple discharge, or a degree of lumpiness sufficient to cause suspicion of cancer) does not carry increased risk for cancer (other than the potential for missing a malignant mass).[28]

Some clinicians differentiate fibrocystic change or disease into those of hyperplasia, adenosis, and cystic change because of their differentiation into age distributions. Hyperplasia characteristically occurs in women in their 20s, often with upper outer quadrant breast pain and an indurated axillary tail, as a result of stromal proliferation. Women in their 30s present with solitary or multiple breast nodules 2–10 mm in size, as a result of proliferation of glandular cells. Women in their 30s and 40s present with solitary or multiple cysts. Acute enlargement of cysts may cause pain, and because breast ducts are usually patent, nipple discharge is common with the discharge varying in color from pale green to brown.[29]

Conditions with increased risk of malignancy include ductal hyperplasia without atypia. This is the most commonly encountered breast biopsy result that is definitely associated with increased risk of future development of breast cancer and confers a 2-fold increased risk. The number, size and shape of epithelial cells lining the basement membrane of ducts are increased, but the histology does not fulfill criteria for malignancy. The loss of expression of transforming growth factor-β receptor II in the affected epithelial cells is associated with an increased risk of invasive breast cancer.[30]

A number of other benign lesions also confer a roughly 2-fold increased risk for development of breast cancer. These include sclerosing adenosis, where lobular tissue undergoes hyperplastic change with increased fibrous tissue and interspaced glandular cells, diffuse papillomatosis which is the formation of multiple papillomas, and fibroadenomas with proliferative disease, which are tumors that contain cysts greater than 3 mm in diameter, with sclerosing adenosis, epithelial calcification, or papillary apocrine change. Radial scars are benign breast lesions of uncertain pathogenesis, which are usually discovered incidentally when a breast mass is removed for other reasons. Radial scars are characterized by a fibroelastic core from which ducts and lobules radiate.[31]

Atypical hyperplasia of either ductal or lobular cells, where the cells are uniform but have lost their apical-basal cellular orientation, confers a 4-fold increased risk unless there is also a family history of 1 or more first-degree relatives with breast cancer, where the risk increases to 6-fold. HER-2/

Table 2. Breast Imaging and Reporting Data System (BI-RADS)*

Category	Interpretation	Probability of Malignancy
0	incomplete; needs additional imaging	n/a
1	negative; nothing to comment on	0%
2	benign finding	0%
3	probably benign finding; short interval follow-up	<2%
4	suspicious abnormality; biopsy recommended	2–75%
5	highly suggestive of malignancy; action demanded	>75%

* Orel SG, Kay N, Reynolds SC, Sullivan DC. BI-RADS categorization as a predictor of malignancy. *Radiology*. 1999;211:845.

neu is a proto-oncogene with intrinsic tyrosine kinase activity. Women with atypical hyperplasia with over-expression of HER-2/neu have a greater than 7-fold increased risk of developing invasive breast carcinoma, as compared with women with non-proliferative benign breast lesions and no evidence of HER-2/neu amplification.[32]

Nipple discharge is often of concern to women and their physicians as a sign of malignancy, but the reality is that non-bloody nipple discharge and bilateral nipple discharge are usually of benign causation. Women with papillomas often have bloody discharge. Nipple discharge is uncommon in invasive breast cancer and if present is invariably unilateral and is usually associated with a palpable mass.[33]

Similarly, breast pain is an uncommon presentation of breast cancer. In a study of 987 women referred for breast imaging because of breast pain alone, only 4 women (0.4%) were found to have invasive breast cancer, a number that was not different from a control asymptomatic group.[34]

DETECTION OF BREAST CANCER

As breast cancer rarely causes pain, a painless mass is much more worrisome for malignancy than is one causing symptoms. Mammography done yearly beginning at age 40 is the current recommendation for women with no risk factors.[35] The most commonly encountered categorization of mammography findings is summarized in Table 2. Although mammograms may detect malignancy as small as 0.5 cm, 10% to 20% of malignancies elude detection by mammography, even when they occur at a much larger size.[36] In a patient with a solid, dominant mass (suspicious mass) the primary purpose of the mammogram is to screen the normal surrounding breast tissue and the opposite breast for non-palpable cancers, not to make a diagnosis of the palpable mass.[8] Thus, a negative mammogram is no guarantee of absence of malignancy, and a mass that does not disappear or collapse with aspiration must be assumed to be a malignancy and biopsied.

DIAGNOSING BREAST CANCER: THE BIOPSY

There are 3 methods of obtaining material from a suspicious breast lump. Fine-needle aspiration is not a reliable means of diagnosis, because it cannot distinguish ductal carcinoma in situ from invasive cancer and it may lead to a false-negative result.[1] Fine needle aspiration (FNA) is generally reserved for palpable cyst-like lumps visible on a mammogram or ultrasound. False positives are negligible but false-negative results occur in 15% to 20%, leading to the recommendation that if the cyst or lump doesn't disappear with FNA, further biopsy is mandatory.[8]

Core needle biopsy has generally replaced fine needle aspiration in all but obvious cysts. Core needle biopsies fail to identify areas of invasion in approximately 20% of cases which are originally diagnosed as ductal carcinoma

Table 3. Bloom-Richardson System With Nottingham Modification Scoring*

Description	1	2	3
Mitotic count	few	(—)	many
Tubule formation	>75% of tumor	(—)	<10% of tumor
Pleomorphism	minimal variation	(—)	marked variation
A total grade of 3 is most favorable, and a total grade of 9 is least favorable			

* Elston C, Ellis I, eds. *The Breast*. Vol 13. Churchill Livingston; 1998.

in situ. Atypical ductal hyperplasia in a core needle biopsy has a relatively high incidence of coexistent carcinoma (approximately 50%). This diagnosis, therefore, demands excisional biopsy.[37]

Seventy-five percent to 80% of excisional biopsies are expected to be benign. Of the remaining 20% to 25% that reveal cancer, a second surgery is often needed to ensure removal of all cancerous tissue.

Axillary lymph node involvement is the most important routinely-available predictor of relapse and of survival.[38] See later discussion on cyclin E measurements and DNA microarrays that may challenge this statement in the future. Axillary recurrence or tumor involvement in internal mammary or supraclavicular lymph nodes always indicates a poor prognosis.[39] Sentinel lymph node biopsy is a biopsy of level I axillary lymph nodes. It has a positive predictive value approaching 100%, with a sensitivity of 89% and a specificity of 100%.[40] Three percent of positive sentinel nodes, however, are found in non-axillary regions. There appears to be a 15% incidence of ''skip'' metastases, defined as metastases to level II and III axillary nodes without involvement of level I nodes.[38] Thus, the cost of performing sentinel node biopsy alone is reflected in a study in which the 10-year survival rate of 85% for stage I breast cancer patients who have full axillary dissection falls to 66% when axillary dissection was not performed.[41] A more complete discussion of sentinel lymph node biopsy can be found in a recent issue of this journal.[42]

High nuclear grade (high nucleus-to-cytoplasmic ratio), high mitotic index and poorly differentiated all connote poor prognosis (see Table 3 for the most commonly used and useful histopathologic scoring system). Infiltrating ductal carcinoma is by far the most common type of invasive breast cancer, with relatively poorer survival. (See Figures 1 and 2) Tubular, medullary, mucinous, and papillary cancers have a more favorable prognosis, but account for only 6% of invasive cancers.[39] Peritumoral lymphatic and blood vessel invasion connotes a much poorer prognosis.

Estrogen and/or progesterone receptor-positive tumors have a better prognosis and a better response to hormone treatment than receptor-negative tumors. Flow cytometry measures DNA Index (or DNA content), with diploid cancer cells (normal DNA content, DNA index of 1) having a better prognosis than those with aneuploidy.[43] S-phase fraction refers to the number of cells actively synthesizing DNA. Tumors with high S-phase cells have a poorer differentiation and poorer prognosis.[44]

Tumor marker CA 15–3 is increased in many women with metastatic breast cancer. HER-2/neu oncoprotein (also called c-erbB-2) is associated with shorter survival, shorter time-to-relapse, and an overall worse prognosis.[1] This tumor marker is especially important with the introduction of trastuzumab for treatment. CA 27.29 is the first FDA-approved (in June 1996) blood test for breast cancer recurrence.

A recent study[45] found that the hazard ratio for breast cancer death in patients with high levels of total cyclin E in the tumor was higher than any other biological marker, including the presence of lymph node metastases (7 times higher), hormone-receptor status, and levels of HER-2/NEU. Among 114

patients with Stage I breast cancer, none of the 102 patients with low levels of cyclin E in the tumor had died of breast cancer 5 years after diagnosis, whereas all 12 patients with a high level of low-molecular-weight cyclin E had died of breast cancer within that period. The hazard ratio for death in breast cancer patients with high total cyclin E levels as compared to those with low levels was 13.3, 8 times as high as the hazard ratio for other clinical and pathologic risk factors.

More recently, DNA-microarray data showed the gene-expression profile is a more powerful predictor of outcome for young patients with breast cancer than the previously standard systems based on clinical and histologic criteria. Patients with a poor-prognosis signature had an overall 10-year survival rate of 54.6%; those with a good-prognosis signature had an overall 10-year survival rate of 94.6%. These data seem to indicate that currently used criteria misclassify a significant number of patients. These data indicate hematogenous metastasis to distant sites may be independent of lymphogenic metastases, and that such tumorigenesis is an early and inherent genetic property of breast cancer.[46]

If verified, these studies should accurately identify patients most likely to benefit from adjuvant treatment.[47]

INTRADUCTAL (DUCTAL) CARCINOMA IN SITU (DCIS)

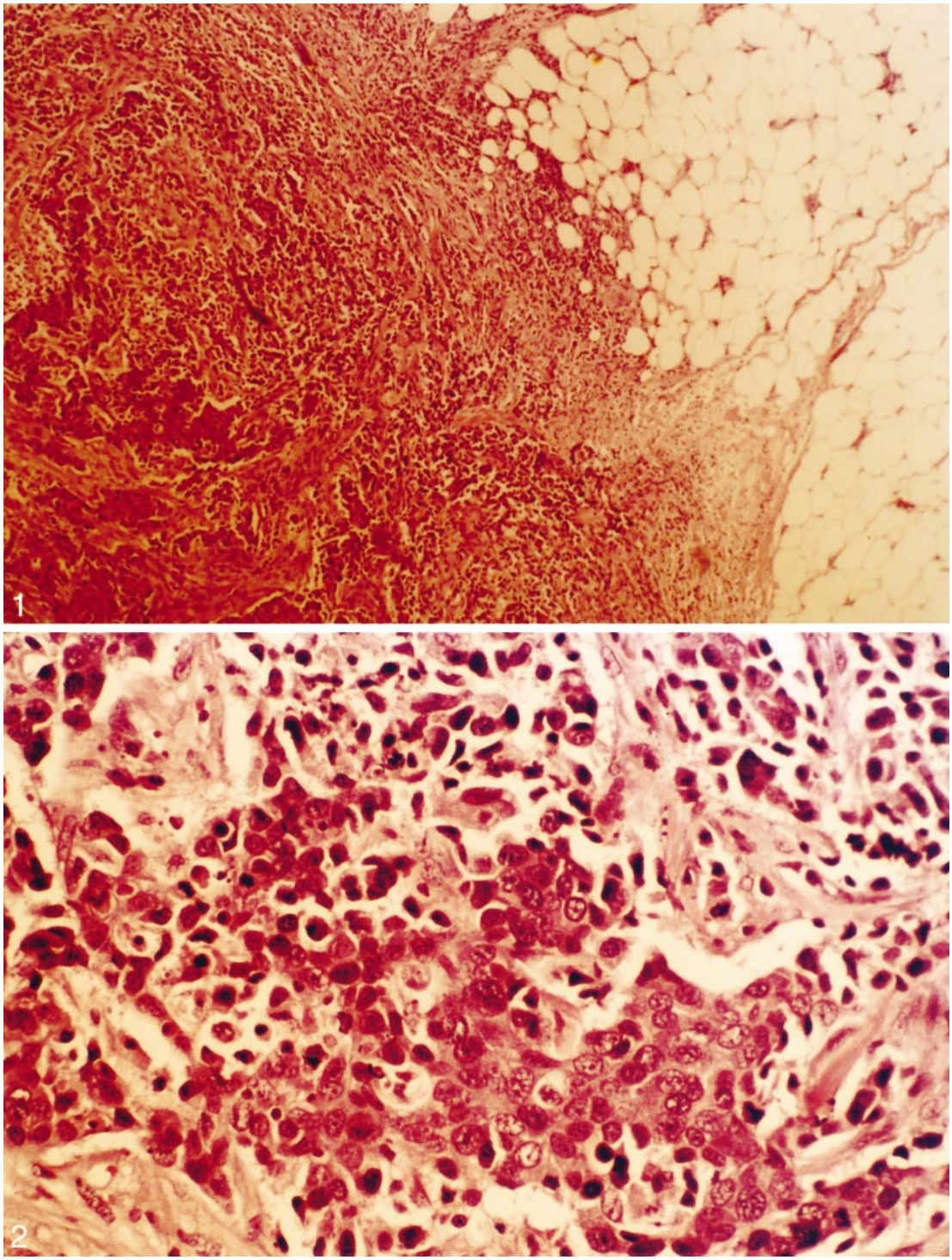
Intraductal (or ductal) carcinoma in situ (DCIS) is the proliferation of malignant epithelial cells confined to ducts, with no evidence of invasion through the basement membrane. Prior to mammography, DCIS was an uncommon diagnosis. With the introduction of routine mammography, the age-adjusted incidence of DCIS rose from 2.3 to 15.8 per 100,000 females, a 587% increase. New cases of invasive breast cancer increased 34% over the same time period.[48]

About 85% of all intraductal cancers, often less than 1 cm, are discovered by the appearance of clustered microcalcifications on mammography. Other conditions, including sclerosing adenosis and atypical ductal hyperplasia, may also present on mammography with microcalcifications. Morphology of the microcalcifications is the most important factor in differentiating benign from malignant calcification. Findings suggesting malignancy include heterogenous clustered calcifications, fine linear branching calcifications, or calcifications in a segmental distribution. Magnification views of benign findings often show multiple clusters of finely granular microcalcification, whereas those associated with DCIS usually appear as coarser microcalcifications.[49]

For women with poorly differentiated DCIS, the microscopic extent of disease correlates well with the radiographic extent. In contrast, the mammographic appearance of well-differentiated DCIS can substantially underestimate the microscopic extent. Residual microcalcifications on the post-surgery mammogram indicates residual tumor with a positive-predictive value of 65% to 70%.[50] The likelihood of residual cancer increases to 90% if greater than 5 microcalcifications are seen on post-operative mammography.[51]

Occult invasion is more common if the lesion is clinically palpable compared to one found only by mammography. In 70 women with palpable DCIS, invasive cancer was found in 6 of 54 (11%), vs none of 16 with non-palpable DCIS.[52] If DCIS diagnosis is made by needle biopsy (note that pathologists may have difficulty distinguishing DCIS from highly atypical hyperplasia), areas of invasive cancer are found in 20% of cases at subsequent surgical excision.[37]

Axillary node involvement in DCIS is distinctly uncommon. In a National Center Data Base review of 10,946 patients with DCIS who underwent axillary node dissection between 1985 and 1991, only 3.6% had axillary metastases.[53] In another series of 189 women with DCIS all of whom underwent axillary node dissection, none had positive nodes.[54] Some experts have argued that presence of axillary lymph node metastases in DCIS means that the pathologist missed the stro-

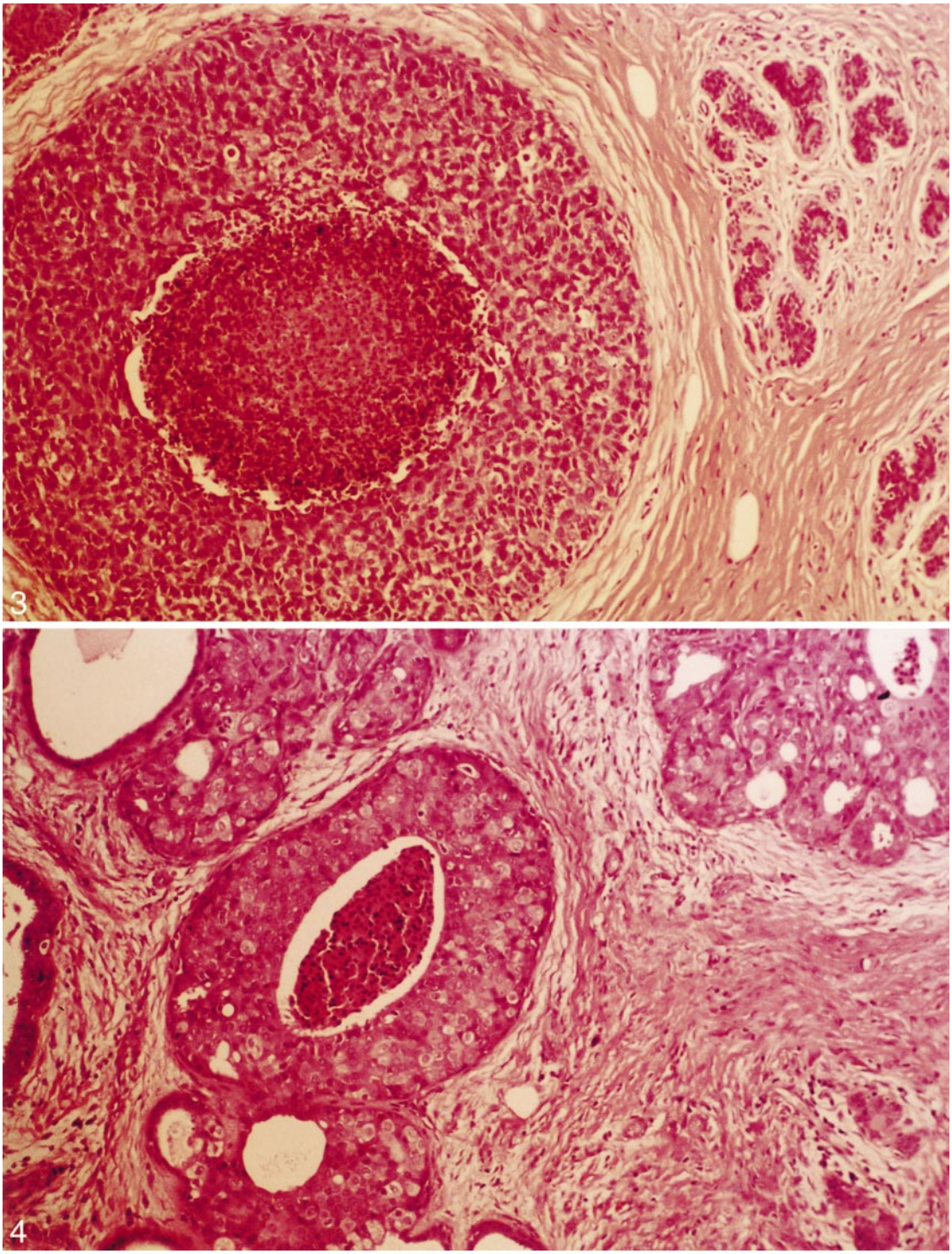


Figures 1 and 2. *Low-power (Fig. 1) and high-power (Fig. 2) views demonstrating poorly differentiated infiltrating adenocarcinoma. The disorganized pattern is characteristic of a poorly differentiated cancer. Photomicrographs courtesy of E. Morrison, MD, Waco, TX.*

mal invasion on initial reading of the pathologic material.

Comedo-type DCIS (Figures 3 and 4) is more malignant than other types of DCIS and is probably mid-way between DCIS and invasive cancer. Invasive breast cancer was ultimately found in 12 of 19 cases (63%) of DCIS with comedo necrosis, vs 4 of 36 (11%) without comedo necrosis.[55]

An on-going controversy among breast



Figures 3 and 4. *Low-power (Fig. 3) and high-power (Fig. 4) views show ductal carcinoma in situ, comedo-type (comedocarcinoma). The tumor is contained within the basement membrane. Central necrosis is characteristic of comedocarcinoma. Photomicrographs courtesy of E. Morrison, MD, Waco, TX.*

surgeons and pathologists is the so-called micro-invasive DCIS lesion. The American Joint Committee on Cancer (AJCC) defines microinvasion as the extension of cancer cells beyond the basement membrane into adjacent tissues, with no focus more than 0.1 cm in greatest dimension. Lesions that fulfill such criteria are staged as $T1_{mic}$, a subset of T1 breast cancer.[56] Ideally, the term microinvasion in the breast should be applied in the

same way as it is in the cervix, ie, to identify those invasive lesions of such limited extent that have virtually no risk of metastases. Unfortunately, the available data are inadequate to permit the reproducible identification of such a subset.

In considering treatment of DCIS, mastectomy is nearly curative (98%).[57,58,59] Breast-conserving therapy (''lumpectomy'') is almost as curative if certain criteria are met: the lesion is <3 cm, the histologic margins are negative, and the nuclear grade is low or intermediate, or at least certainly not high grade.[60] Most commonly, breast-conserving surgery is followed by radiation. The rate of local failure in the treated breast is 16% at 15 years, with the median time to local failure being 5.0 years (mean 5.7 years, range 1.0–15.2 years).[61]

The importance of age and margin status in treating DCIS was revealed in a study of 418 women who underwent breast-conserving surgery (''lumpectomy'') and breast radiation. Recurrence occurred in 48 (11%) within 10 years. Recurrence developed in 24% of women who retrospectively had positive margins, 12% in women with unknown margin status, and 9% of women with negative margins. The likelihood of local recurrence is statistically related to age of the woman at initial diagnosis and surgery, with recurrences of 31% for those less than 39 years of age, 13% for ages 40–49, 8% for ages 50–59, and 6% for those older than age 60 ($p = 0.0001$).[61]

When local recurrence does occur following lumpectomy and radiation for DCIS, roughly half of the women again have DCIS and half have invasive ductal carcinoma. Salvage therapy for recurrence usually consists of mastectomy (88%) without adjuvant chemotherapy or tamoxifen (69%), and at 8 years post salvage treatment in 1 series, 92% of patients were alive and 88% were free of any evidence of recurrent disease. Favorable prognostic factors after salvage treatment were DCIS as the histology of the local recurrence and mammography only as the method of detection of the local recurrence.[62]

Interestingly, a diagnosis of DCIS vs the more ominous invasive ductal breast cancer does not automatically imply a simpler surgical solution. In 1 series, contraindications to breast preservation surgery were present in 33% of women with DCIS, compared to only 10% of women with stage I invasive ductal carcinoma.[63]

Two randomized trials have compared lumpectomy alone for DCIS with lumpectomy with radiation.[64,65] Both trials favored lumpectomy with radiation in regard to recurrence of malignancy (whether the recurrence was DCIS or invasive ductal disease), but overall survival of the 2 groups was similar (95% vs 94%), a reflection of the efficacy of salvage mastectomy. There appears to be a select group of patients with DCIS who have low histologic grade, absence of comedo-type necrosis and small tumor size, who can be managed with lumpectomy alone.[66] The time course to local failure is usually prolonged, and when local failure occurs, invasive cancer is present in the same one-half of cases as occurs with lumpectomy with radiation therapy.[62,67,68]

Tamoxifen is indicated for women with DCIS who have undergone either lumpectomy or lumpectomy with radiation. In a trial to specifically address this issue, 1804 women with DCIS undergoing breast conservation therapy were randomly assigned to receive either tamoxifen (20 mg daily for 5 years) or placebo. After a mean follow-up of 62 months, tamoxifen reduced the rate of invasive recurrence from 9 to 5 per 1000 patients (relative risk reduction 0.56, $p = 0.03$) and reduced the rate of recurrent DCIS from 11% to 9% per 100 patients (relative risk reduction 0.82, $p = 0.043$). Overall, the ipsilateral recurrence of either local or invasive cancer was reduced from 13% to 8% at 5 years in the tamoxifen group.[65]

LOBULAR CARCINOMA IN SITU (LCIS)

As it is clinically undiagnosable (it is never a palpable mass and it has no distinguishing mammographic features), the true incidence

of LCIS is unknown.[69] LCIS incidence in breast masses removed has varied from 0.05% to as high as 10%,[70,71,72] and the incidence of LCIS is 10-fold higher in white compared to African-American women in the United States.[73] This diagnosis is always made incidental to a needle biopsy or resected mass done for fibrocystic change, fibroadenoma, or a mass suspected as being cancer.[74] LCIS is more often detected in premenopausal than postmenopausal women, suggesting a hormonal influence in the development or maintenance of these lesions.[75,76]

LCIS requires no specific therapy per se. Although the cells of LCIS are in fact small, well-differentiated neoplastic cells, they do not behave as a true malignant neoplasm in that these cells may distend and distort the terminal-lobular units, but invasion of and through the basement membrane does not occur, so the lesion never results in invasive breast malignancy.

Rather, the clinical significance of LCIS is that it serves as an important marker for subsequent invasive breast cancer, in a magnitude of risk of approximately 1% per year for the remainder of the woman's life (7- to 10-fold higher risk of invasive breast cancer than the average US woman[27]), with the invasive cancer occurring with equal frequency in either breast. Subsequent invasive cancers are also more often of the infiltrating ductal type.[75]

The recommended management of LCIS is careful follow-up and semiannual physical breast exam and yearly mammography. The NSABP tamoxifen prevention trial (NSABP protocol P1) included 826 women with LCIS. At 4 years of follow-up, invasive breast cancer was less common in the tamoxifen arm (2% vs 4% with placebo, 5.7 vs 13 per 1000 women, a 56% risk reduction).[77] However, many experts do not recommend tamoxifen in this group, citing the adverse effects of tamoxifen (hot flashes, an estrogen antagonist effect, and in postmenopausal women the increased occurrence of endometrial cancer and venous thromboembolism) and costs (tamoxifen is given in 20 mg tablets daily for 5 years).

Table 4. TNM Definitions and Staging

TNM	Description
T_{is}	Carcinoma in situ
T1	Tumor 2 cm or less in greatest dimension
T1a	0.5 cm or less
T1b	>0.5 cm but ≤ 1 cm
T1c	>1 cm but ≤ 2 cm
T2	Tumor > 2 cm but ≤ 5 cm
T3	Tumor > 5 cm
T4	Tumor of any size with direct extension to chest wall, skin
N0	No regional lymph node metastases
N1	Metastases to moveable ipsilateral axillary lymph nodes
N2	Metastases to fixed ipsilateral axillary lymph nodes
N3	Metastases to ipsilateral internal mammary lymph nodes
M0	No distant metastases
M1	Distant metastases (including supraclavicular lymph nodes)

TNM Stage

Stage	Description
0	T_{is}, N0, M0
I	T1, N0, M0
IIA	T0, N1, M0 *or* T1, N1, M0 *or* T2, N0, M0
IIB	T2, N1, M0 *or* T3, N0, M0
IIIA	T0–T2, N2, M0 *or* T3, N1, M0
IIIB	T4, any N, M0, *or* any T, N3, M0
IV	any T, any N, M1

STAGING AND PROGNOSIS OF BREAST CANCER

At initial diagnosis, over 50% of breast cancers are stages 0 or I,[78] and 75% are Stage 0, I, or II. (Table 4)[79]

The quantity of lymph node involvement has a profound impact on survival. Stage IIA cancer (T0-T1, N1) with only 1 involved lymph node has a 10-year disease-free survival of 71% and a 20-year disease-free survival of 66%. If 2 to 4 lymph nodes are involved, the 10-year disease-free survival is 62% and the 20-year disease-free survival is 56%.[79]

SURGICAL TREATMENT OF BREAST CANCER

The Consensus Development Conference on the Treatment of Early-Stage Breast Cancer (June 1990, NCI) has concluded that breast conservation treatment is an appropriate method of primary therapy for the majority of women with Stage I and Stage II breast cancers. This treatment is preferable in many cases because it provides survival equivalent to total mastectomy and axillary dissection while preserving the breast.[80]

Subsequent studies have confirmed that there is no difference in long-term survival between surgical removal of the breast (mastectomy) and excision of the tumor mass and radiation therapy to residual breast tissue (breast conservation therapy).[81–83]

Breast-conserving surgery includes lumpectomy, re-excision, partial mastectomy, quadrantectomy, segmental excision, and wide excision. Axillary lymph nodes are removed for evaluation through a separate incision. The most common breast-removal procedure is a modified-radical mastectomy, which involves making an elliptical incision around an area including the nipple and biopsy scar, removing that section, and tunneling under the remaining skin to remove the breast tissue and some lymph nodes. Radical mastectomy, which removes the entire breast, chest wall muscles, and all axillary lymph nodes, is rarely done today because it offers no survival advantage over a modified radical mastectomy. A simple, or total mastectomy, removes the entire breast but none of the axillary lymph nodes. This is usually done for women with DCIS, or prophylactically for women at especially high risk for developing breast cancer. A newer procedure is the skin-sparing mastectomy, which involves removing the breast tissue through a circular incision around the nipple and replacing the breast with fat taken from the abdomen or back.

ADJUVANT THERAPIES FOR BREAST CANCER

Radiation adjuvant therapy is routine after breast-conserving surgery (eg, lumpectomy) to prevent recurrence of cancer in the breast, and it may be used after mastectomy to prevent recurrence on the chest wall and axilla. Radiation therapy is generally given 5 days a week over a 5- or 6-week time span, with care taken to try to avoid damage to the heart or lungs. The only usual changes with breast radiation are skin erythema and possibly some transient lymphedema.

Table 5. Standard Adjuvant Chemotherapy Regimens

Standard Regimens	Components
AC (w or w/o T)	Adriamycin, cyclophosphamide, Taxol
CMF	Cyclophosphamide, methotrexate, fluorouracil (5-FU)
CEF	Cyclophosphamide, epirubicin, fluorouracil (5-FU)
CAF	Cyclophosphamide, adriamycin, fluorouracil (5-FU)

Systemic adjuvant chemotherapy is never recommended for non-invasive, in situ cancer (DCIS). The most commonly used standard adjuvant chemotherapy regimens are listed in Table 5.

Hormone adjuvant therapy helps to prevent recurrence by blocking the effects of estrogen, which is known to stimulate cancer cell growth. Hormones are most effective in women whose primary tumor has hormone receptors (ie, estrogen-receptor or progesterone-receptor positive). Tamoxifen is the standard first choice of most experts.[84] Other hormonal therapeutic agents include aromatase inhibitors, which interfere with the enzyme aromatase, which plays a critical role in the production of estrogen in postmenopausal women. Examples of this class include anastrozole, letrozole and exemestane.[85,86]

A recent study of women who had completed 5 years of tamoxifen therapy and were assigned to either no therapy or continuing therapy with letrozole was prematurely ended when preliminary results revealed a greater than 40% reduction in recurrent breast cancers in the letrozole arm. Unanswered

questions are whether women should take letrozole for 5 years (the original study design) or indefinitely, and whether women should take letrozole (or one of the other aromatase inhibitors) instead of tamoxifen initially. An earlier head-to-head comparison of anastrozole and tamoxifen found that it was somewhat more effective in reducing the risk of a recurrence than tamoxifen.[99]

Biological adjuvant therapy includes trastuzumab, which blocks the action of a growth-promoting protein called Her-2/neu that is found in larger-than-normal amounts in about 30% of breast cancers.[87] Trastuzumab more specifically targets cancer cells and thus has fewer side effects than standard chemotherapy, although it may have some effects on normal heart tissue when used with chemotherapy.[88] The drug has been approved for metastatic breast cancer and is currently under study as a first-line agent in combination with other chemotherapy.[89]

PATTERNS OF RELAPSE

The rate of local recurrence at 8 to 10 years has varied from 4% to 20%, with no differences between women who underwent mastectomy vs those who underwent breast-conserving therapy. However, the mortality implication of recurrence between the 2 groups is considerable. Women treated initially with breast-conservation therapy can present with locoregional recurrence in the preserved breast tissue. This may represent regrowth of the previous tumor or a second primary tumor. These patients can often be treated with mastectomy for curative intent. Women who have undergone a mastectomy as a primary treatment will usually manifest locoregional recurrence as a mass in the chest wall or overlying skin. This carries a much graver prognosis, since distant metastatic disease is already present in 25%–30% of these cases.[90]

Breast cancer survivors are at increased risk for developing a second primary breast cancer compared with the general population (approximately 0.5% to 1% of women per year develop contralateral breast cancer).[91] Patients who have undergone breast conservation therapy are at similar risk for developing a second primary breast cancer in the preserved breast as in the contralateral breast.

Finally, in addition to locoregional recurrence and second primary breast cancer, relapse may occur with the presence of distant metastases.

RECOMMENDED SURVEILLANCE IN BREAST CANCER SURVIVORS

One trial randomly assigned breast cancer survivors to either a specialist or a family physician, and found no differences between the 2 groups in measured outcomes, including time to diagnosis of recurrence, anxiety, or health-related quality of life.[92] A subsequent economic analysis of this study found the quality of life as measured by frequency and length of patient visits and costs were better when follow-up was provided by the family physician as compared to the specialist.[93]

Routine history and physical examination and regularly scheduled mammograms are the mainstay of care for the breast cancer survivor.[94] Recurrence of breast cancer is more frequently discovered by the patient (71%) than by her physician (15%).[6] Women should be encouraged to perform breast self examination monthly. Mammograms should be done at 6 and 12 months after surgery and then yearly thereafter.

Several tumor-associated antigens, including CA 15-3 and CEA, may detect breast cancer recurrence, but not with sufficient sensitivity and specificity to be routinely used by either clinicians[95] or insurance underwriters. A newer marker, CA 27.29, showed promise in one well-designed study of 166 women with stage II and III breast cancer. The sensitivity and specificity of this test were 58% and 98%, respectively. Recurrence was detected approximately 5 months earlier than with routine surveillance.[96] However, improvement in survival or quality of life using this marker has not yet been proven.

Neither routine chest x-rays nor serial ra-

dionucleotide bone scans have been found to be useful in detecting metastatic disease in asymptomatic women.[97,98]

CONCLUSION

Although breast cancer is a major cause of morbidity and mortality in women, and thus is of understandable concern to life underwriters, basic understanding of the disease often allows for aggressive underwriting in some cases. Women with DCIS and LCIS who have been correctly managed should still be eligible for optimistic ratings, whereas underwriting women with cumulative risk factors described in this treatise, as well as unfavorable pathology and especially the presence of axillary metastases, calls for ever increasing caution.

Of particular note to underwriting departments is the newer reports of the discriminating power of measurements of cyclin E and analysis of the levels of expression of thousands of genes simultaneously with the use of DNA microarray technology in identifying women with stage I and II breast cancers with both much better, and those with much worse, prognoses than is now available with knowledge of estrogen-receptor status and the presence or absence of lymph node metastases.

In the section Risk Factors for Development of Breast Cancer, we have reviewed the data available at the time of this writing on the controversial role of hormone replacement therapy (HRT) in post-menopausal women. Although some controversial points remain, there does appear to be mounting evidence that HRT that includes both estrogen and progestin does entail risks that need to be considered in underwriting decisions.

Perhaps the most significant finding in our review was that 70% to 75% of women with invasive breast cancer actually die of something other than their breast malignancy. Although there are certainly red flags that should raise serious concern in underwriting these women, there are many ''breast cancer survivors'' who are just that: they apparently have survived their disease. But only a firm understanding of all of the issues described in this review will allow for the selection of these insurable cases.

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