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ORIGINAL ARTICLE

Premalignant Disease: The Breast

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Premalignant disease of the breast is a controversial and evolving area of medical research. Breast cancer remains the number one cause of death in women in the US between the ages of 40 and 55 and ultimately causes about 4% of all deaths in women. Efforts to identify women at increased risk are of tremendous importance both clinically and from an insurance perspective. To make appropriate underwriting decisions, we need to evaluate proposed markers of increased risk with respect to what is known about how they affect short-term and/or long-term mortality.

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This is the third in a series of 4 articles on premalignant disease. Please refer to "Underwriting Implications of Premalignant Disease" in the February 1998 issue of *Risk Insights* for background information and clarification.

In the United States, breast cancer is the most common cancer in women and is responsible for approximately 46,000 deaths per year. One in 8 women will develop breast cancer, and breast cancer is ultimately responsible for approximately 4% of deaths in women. Breast cancer remains the leading cause of death in women aged 40–55 years, even though half of breast cancer diagnoses are made after the age of 65. Clearly, any method of identifying and treating high-risk groups has the potential for enormous impact on mortality.

The breast is a secretory organ composed of ducts that branch into ever-smaller ductules and finally terminate in the milk-producing lobules. The epithelial lining of the lobules and ducts gives rise to the vast majority of breast cancers. Pathologists use the terms ductal and lobular to indicate where a tumor originates. The breast is a solid organ; therefore, there is no simple way to examine the epithelium, and as of today there is no biochemical marker adequate for screening purposes. Breast cancer screening at this time remains dependent on physical examination and screening mammography. In other words, biopsy of the breast is performed either for abnormal physical findings (a palpable mass) or for abnormal mammographic findings.

FIBROCYSTIC BREAST CHANGES

Breast biopsies can be categorized as benign, premalignant, or malignant. The benign category includes a variety of findings generally referred to as pathological fibrocystic breast changes. Pathological fibrocystic changes are found in 40% to 90% of women according to estimates based on autopsy studies. There has been controversy over which, if any, of these findings is associated

Fibrocystic Breast Changes, Associated Cancer Risk, and Findings

Category	Cancer Risk	Findings
Clinical fibrocystic changes (history and physical exam findings)	No increased risk	Affect majority of women; painful or tender breasts; nodular or lumpy breasts; cysts; peak ages 30 to 50
Pathologic fibrocystic changes (biopsy findings)		
Nonproliferative changes	No increased risk	Adenosis; cysts; duct ectasia; mastitis; fibrosis; mild hyperplasia; metaplasia; fibrosis
Proliferative changes without atypia	1.5 to 2 times relative risk	Moderate hyperplasia; florid hyperplasia; papillomas; fibroadenoma; sclerosing adenosis
Proliferative changes with atypia	4 to 6 times relative risk	Atypical ductal hyperplasia; atypical lobular hyperplasia

with a significant increase in cancer risk, and some entities have been alternately considered either high or low risk according to conflicting study results. The Table shows a list of clinical fibrocystic changes, findings common in benign breast biopsies, and their associated relative risk of breast cancer.[1,2]

Nonproliferative lesions are not associated with an increased risk of cancer. Proliferative fibrocystic changes without atypia may carry some small increased risk of cancer. Some of these lesions, such as sclerosing adenosis, have been very controversial but are not generally considered to confer a >2-fold relative risk. This may seem like a worrisome increase in risk, but this increase is similar to the increased risk of a woman whose mother had breast cancer after age 70. From an underwriting standpoint, only high-risk lesions will have an appreciable mortality impact.

ATYPICAL HYPERPLASIA

Proliferative fibrocystic changes with atypia represent a different level of risk. These changes constitute a diagnosis of intraepithelial neoplasia or dysplasia and as such are characterized by increased numbers of cells (hyperplasia) as well as nuclear and architectural abnormalities (atypia). Pathologists have chosen to use the terms *atypical ductal hyperplasia (ADH)* and *atypical lobular hyperplasia (ALH)* when referring to these lesions. ADH and ALH are much less common than other fibrocystic changes and are found in approximately 3% to 4% of breast biopsies.

The breast, like the prostate, is a solid organ, which makes it virtually impossible to identify and serially biopsy the same lesion. As a result, the identification of increased risk after a diagnosis of ALH or ADH rests on epidemiological evidence, pathological criteria, ploidy, and genetic studies. The research strongly suggests that the atypical hyperplasias are distinct from other benign breast lesions and represent a true neoplastic proliferation.

The importance of ADH and ALH for clinicians and underwriters is that a diagnosis of either one is a powerful risk factor for adenocarcinoma. Most studies estimate the relative risk to be in the range of 4- to 6-fold, which translates to an 8% risk of breast cancer over the 15 years after diagnosis. The risk is essentially doubled again to approximately 11-fold if a woman has a first-degree relative (mother, sister, daughter) who has had breast cancer. In this setting, the risk of breast cancer over the ensuing 15 years would be close to 20%.[3]

CARCINOMA IN SITU

The higher grades of premalignant disease of the breast are ductal carcinoma in situ (DCIS) or intraductal cancer and lobular carcinoma in situ (LCIS) or lobular neoplasia. Before the advent of mammography, only

DCIS that formed a palpable mass could be detected. At that time, DCIS constituted ≤5% of all breast cancer diagnoses. Since mammography became an accepted screening test, the number of diagnoses of DCIS has soared because of the fact that DCIS often forms characteristic microcalcifications. DCIS now constitutes approximately 15% to 20% of all breast cancer diagnoses and partially accounts for the increased incidence of breast cancer seen in the 1980s and 1990s.

DCIS is a term used to describe lesions that have all the cellular features of ductal carcinoma but that show no evidence of invasion. DCIS behaves like a true premalignant lesion. It is generally located in the same portions of the breast as invasive cancer and, in cases in which DCIS has been followed, subsequent invasive cancers are typically in the same location as the preceding DCIS.

As with other premalignant lesions, there is no exact point of delineation between ADH and DCIS but rather a continuum of pathological change and risk. DCIS itself can be further subcategorized in terms of its severity. The risk of developing invasive disease is increased if it is of a high nuclear grade of tumor and of the comedo subtype.

Clearly, not all carcinomas in situ go on to invasive disease, but we do not have reliable means to identify those that will progress. In the case of DCIS, however, it has been shown that watchful waiting will result in a substantial increase in the breast cancer death rate in those women affected. Furthermore, much of the increased breast cancer risk of DCIS will occur in the first 10–15 years after diagnosis. Overall, untreated DCIS is associated with a breast cancer mortality rate estimated to be in the 10% range at 10 years.

Treatment of DCIS is in a state of evolution. The main treatment options currently are (1) lumpectomy followed by radiation or (2) simple mastectomy. Sometimes after lumpectomy and radiation, salvage mastectomy is necessary for recurrences. Either of these treatments is associated with an excellent prognosis and a breast cancer death rate at 10 years in the 1% range. Wide excision alone is also used but has been shown to be associated with a higher risk of breast cancer recurrence.[4,5] Nonetheless, it may still be used in selected, low-risk situations or in women who refuse more aggressive treatment. Lymph node dissection is rarely indicated because the risk of a positive node in a woman with DCIS is <2%.[6] A great deal of study is currently under way to refine and delineate optimal treatment of DCIS, including a study of lumpectomy with radiation and tamoxifen.

LCIS or lobular neoplasia is an interesting and controversial lesion that can only be found incidentally. While it does not produce any characteristic clinical or mammographic findings by itself, it is sometimes found associated with other benign or malignant masses. LCIS is usually found in premenopausal women and is frequently bilateral. Some authorities contend that the breast cancer rate is low in the first few years after the diagnosis of LCIS. However, the cumulative 25-year rate is still ≥25%.[7] Carcinomas found after a diagnosis of LCIS are just as likely to be in the opposite breast and are more likely to be ductal in origin than lobular. These findings imply that LCIS is a powerful risk factor for cancer but may not in itself constitute the actual premalignant lesion. For this reason, some experts prefer the term lobular neoplasia.

Unfortunately, there is no simple answer for women with LCIS. The most effective option is bilateral mastectomy, but this is obviously problematic. Some women still undergo this procedure, but most patients and physicians prefer watchful waiting.

The mortality risk from a diagnosis of LCIS may be significant, especially given the generally young age at the time of this diagnosis. Some additional rating should be considered in women with untreated LCIS.

The National Surgical Adjuvant Breast and Bowel Project recently interrupted a trial of tamoxifen in women considered at high risk of developing breast cancer because of the importance of the preliminary results. A large majority of the participants had a family history of breast cancer, 6% had a personal

history of lobular neoplasia (LCIS), and 9% had a history of ADH. Overall, the group had a 5-fold relative risk of developing breast cancer. The risk was reduced by almost half for those receiving tamoxifen as opposed to placebo, but thus far there has not been enough detail published to know whether specific subgroups of risk were affected differently. In addition, the study was only run for 4 years, and therefore long-term outcomes are not known. There is concern that perhaps the tamoxifen is only delaying diagnosis.[8] In any case, this is the first time that any preventive treatment has reduced breast cancer risk, and much more information can be expected over the next few years with respect to chemoprevention with tamoxifen and other related drugs such as raloxifene.

CONCLUSION

Premalignant disease of the breast spans a wide spectrum of risk and should be approached in a systematic manner. A careful review of the pathology report is mandatory. Family history may substantially alter risk if atypical hyperplasia is present. Treatment and adequate follow-up should be optimal for the most favorable offers. Younger women, particularly those younger than 45 years, with DCIS, LCIS, or atypical hyperplasia with a family history of breast cancer in a first-degree relative may require a small to moderate rating. In many cases, especially in older women, premalignant disease may be a standard risk.

REFERENCES

1. Bilimoria MM, Morrow M. The woman at increased risk for breast cancer: evaluation and management strategies. *CA Cancer J Clin.* 1995;45:263–278.
2. Marshall LM, Hunter DJ, Connolly JL, et al. Risk of breast cancer associated with atypical hyperplasia of the lobular and ductal types. *Cancer Epidemiol Biomarkers Prev.* 1997;6:297–301.
3. Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. *N Engl J Med.* 1985;312:146–151.
4. Fisher B, Constantino J, Redmond C, et al. Lumpectomy compared with lumpectomy and radiation therapy for the treatment of intraductal breast cancer. *N Engl J Med.* 1993;328:1581–1586.
5. Veronesi U, Luini A, Del Vecchio M, et al. Radiotherapy after breast-preserving surgery in women with localized cancer of the breast. *N Engl J Med.* 1993;328:1587–1591.
6. Parker RG, Berkbigler D, Rees K, Leung KM, Legorreta AP. Axillary node dissection in ductal carcinoma in situ. *Am J Clin Oncol.* 1998;21:109–110.
7. O'Shaughnessy JA. Chemoprevention of breast cancer. *JAMA.* 1996;275:1349–1353.
8. Ault A, Bradbury J. Experts argue about tamoxifen prevention trial. *Lancet.* 1998;351:1107.