Journal of Cellular Biochemistry 17G:59–64 (1993)

Diagnostic Criteria and Cancer Risk of Proliferative Breast Lesions

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Abstract Breast cancer risk assessment in women following a benign breast biopsy is a promising area with regard to intermediate endpoint determination, and has been particularly fostered by the consensus agreement concerning the risk attributed to specific diagnoses [1]. Several recent studies have largely verified this approach [2–4], and a recent report demonstrates general agreement among most expert pathologists regarding diagnostic criteria for these lesions [5]. However, in a limited number of cases, determining exact levels of risk for individual patients has been problematic as a result of a failure by pathologists to achieve consensus on diagnostic criteria for these same lesions. This situation has arisen primarily because it is much more tenable to disagree over subjective diagnostic criteria, than it is to argue with robustly supported epidemiological data. Without agreement on reproducible diagnostic criteria, widely promulgated consensus risk estimates for these specific histologic entities are no longer applicable. In addition, those individuals who choose different diagnostic criteria for proliferative breast lesions fail to realize that the terminology, epidemiological risk estimates, and diagnostic criteria used by Dupont and Page are inexorably linked. Since the publication of the consensus statement [1], those using the terms "atypical ductal hyperplasia" and "atypical lobular hyperplasia" have by default accepted the diagnostic criteria of Dupont and Page. Therefore, surgical pathologists who desire to make use of the consensus risk estimates must familiarize themselves with diagnostic criteria for the various histologic entities that comprise proliferative disease of the breast as defined by Dupont and Page [6]. This presentation will concentrate on the importance of a combined histologic and cytologic approach to diagnose proliferative breast lesions, and will specifically focus on usual hyperplasia, atypical ductal hyperplasia, atypical lobular hyperplasia, and both ductal and lobular carcinoma *in situ*.

Key words: Atypical hyperplasia, breast cancer, cancer risk, hyperplasia, family history, premalignancy, proliferative disease

Since publication of the Consensus Statement of the College of American Pathologists on the relative risk of invasive breast cancer attributable to various histopathologic entities in the breast, there has been an increased realization of the importance of histopathologic assessment of benign breast biopsies [1]. This realization has not come without controversy, but it is strongly supported by a number of recently published reports [2–4] that largely confirm the original studies [6]. This approach has now become standard practice and a key component in determining the magnitude of risk for individual patients (Fig. 1). An essential element of this approach is standardization and widespread acceptance of diagnostic criteria for various histopathologic entities that indicate an elevated risk level for breast cancer development. Although this point is often not properly emphasized outside pathol-

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ogy literature, standardization of diagnostic criteria is crucial if consensus-relative risk levels are to have meaning across institutional borders.

PREMALIGNANT BREAST DISEASE

The concept of premalignant breast disease encompasses a diverse group of histologically defined entities whose common thread is an epidemiologically proven and clinically significant association with increased breast cancer risk. These lesions represent higher risk subgroups of proliferative breast disease as defined by Dupont and Page [6], and include atypical hyperplasias and both ductal and lobular carcinoma *in situ* (DCIS, LCIS). This definition excludes moderate and florid examples of usual hyperplasia, well-developed examples of sclerosing adenosis, and intraductal papillomas (lesions comprising the slightly increased risk category) as components of premalignant breast disease because their level of risk (1.5–2.0×) is not sufficient to warrant changes in clinical practice, and their morphological features do not bear as direct a relationship to fully malignant breast tumors.

It is a common misconception that all lesions identified as a component of premalignant breast disease represent intermediate stages in the development of invasive breast cancer, and as such, constitute direct precursor lesions of invasive breast cancer. In truth, the majority of these lesions are best characterized as indicators of increased risk, not direct precursor lesions [7]. This is a subtle but conceptually important point because it has considerable clinical significance. Lesions defined as general markers of increased risk indicate a risk for breast cancer development in either breast and have no implication with regard to surgical management of these lesions as localized phenomena. Atypical ductal hyperplasia, atypical lobular hyperplasia, and LCIS fall into this category because they predict an elevated breast cancer risk equally divided between both breasts. Therefore, wider local excision or ipsilateral simple mastectomy has no place in the clinical management of these lesions, because any breast cancer that might develop is just as likely to occur in the opposite breast. In contrast, epidemiological evidence strongly suggests that DCIS does represent a non-obligate precursor lesion, because invasive breast cancers that develop after DCIS is identified tend to occur at the same site, providing strong evidence that DCIS is not just a marker of increased risk [8,9]. The concept of DCIS as a true precursor lesion derives solely from epidemiological evidence; there is no experimentally defined pathway of progression from normal epithelial cells to invasive breast cancer. Our inability to define such a pathway is, to some extent, a result of the way we identify premalignant lesions of the breast, *i.e.*, by surgical removal and histological examination. This requirement precludes following the natural history of an undisturbed lesion and renders the experimental determination of a breast cancer progression pathway quite difficult. Unfortunately, no other method offers a reliable means of identifying such lesions [10].

While there are inherent limitations to epidemiological studies, they have proven to be a very powerful way to determine the clinical meaning of specifically defined histologic lesions, representing a great advance over concurrent observational studies. This in no way diminishes the value of such studies. They were unquestionably the logical first step in identifying and defining the most appropriate lesions for detailed epidemiologic study [11–13].

Several recent reports have demonstrated the usefulness of establishing strict histological and cytological criteria for specific breast disease lesions and then determining their cancer risk association. This approach has largely confirmed the original studies of Dupont and Page [6]. In these studies, the diagnostic criteria of Page and Rogers [14] for premalignant breast lesions were used to categorize histological lesions from large cohorts of women with benign breast biopsies. The relative risk estimates that resulted from these studies compared quite favorably to those determined in the Nashville studies [2,3,15]. In addition, a recent report has confirmed the reproducibility of this approach when diagnostic criteria are agreed upon [5]. We therefore believe that if pathologists choose to use the terminology and risk estimates agreed upon by the consensus statement of 1986, they must be fully cognizant of the specific criteria used to diagnose these lesions and employ such criteria in their daily practice.

Details of diagnostic criteria for some common lesions that comprise proliferative breast disease are set out below.

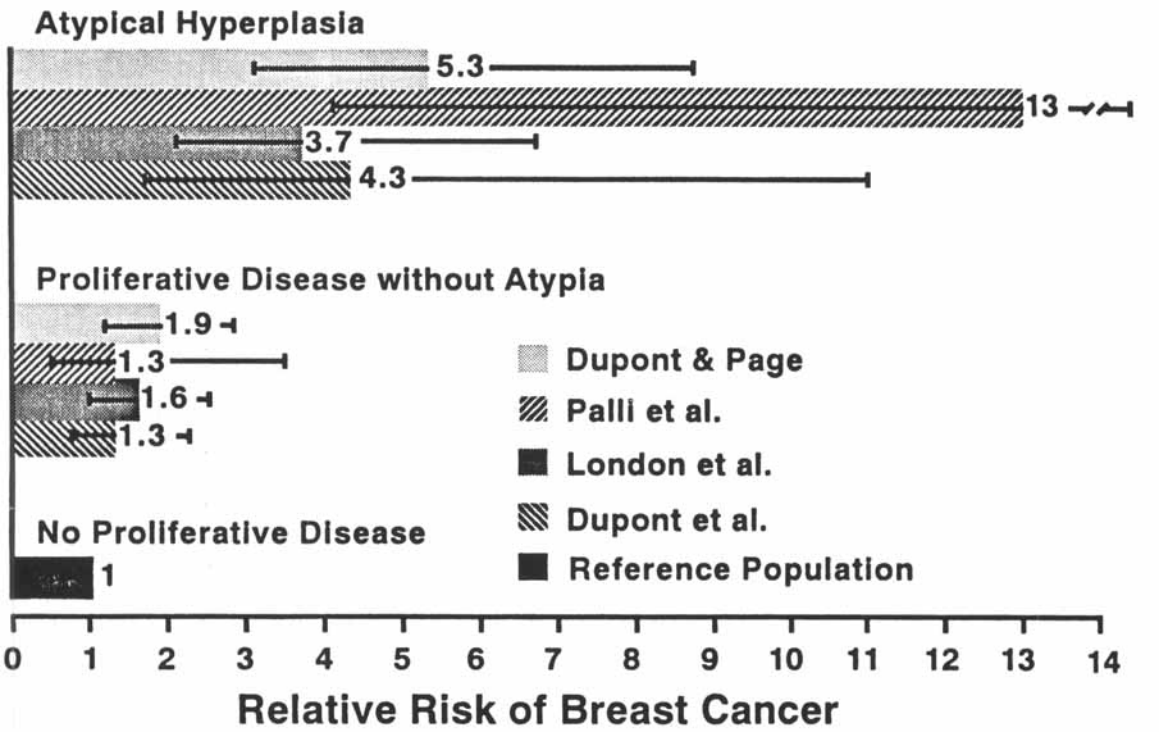

Fig. 1. Relative risks of breast cancer associated with atypical hyperplasia and proliferative disease without atypia that have been reported in the literature. Relative risks are calculated with respect to women who underwent biopsy but did not have proliferative disease. The horizontal black lines denote 95% confidence intervals for these relative risks. See references [2–4,6]. Figure from [2], reproduced with permission from the publisher.

USUAL HYPERPLASIA

Usual hyperplasia is the most common change found in breast biopsies that indicates increased risk for breast cancer development. It is present in over 20% of post-mammographic biopsies. Previous designations for this alteration include "epitheliosis" and "papillomatosis." Over time, these terms have been bastardized by including a wide variety of epithelial alterations under their umbrella. We prefer the term usual or florid hyperplasia, because it emphasizes the commonality of the change.

This epithelial alteration indicates an increased level of risk approximately 1.5- to 2.0-fold over that of control populations. The hallmark of this change is the filling and distention of spaces by a proliferation of epithelial cells exhibiting considerable variability in shape and relationship to one another. Important characteristics found in florid hyperplasia that distinguish this change from atypical ductal hyperplasia or DCIS are variability in nuclear shape and the presence of irregular slit-like spaces. In both atypical ductal hyperplasia and DCIS, the neoplastic cell population tends to be quite regular in its nuclear characteristics and exhibits crisp, uniformly shaped spaces. In addition, florid hyperplasia generally exhibits swirling patterns of cells with irregularly defined cell borders and marked variation in cell placement. Essentially, florid hyperplasia is distinguished from more worrisome lesions by its inherent variability and heterogeneity not only within a single lesion, but also between lesions (Fig. 2).

ATYPICAL DUCTAL HYPERPLASIA AND DUCTAL CARCINOMA *IN SITU*

In contrast to the changes exhibited by florid hyperplasia, the most characteristic feature of atypical ductal hyperplasia or DCIS is uniformity of the neoplastic cell population. In non-comedo DCIS, the diagnosis requires a uniform popula-

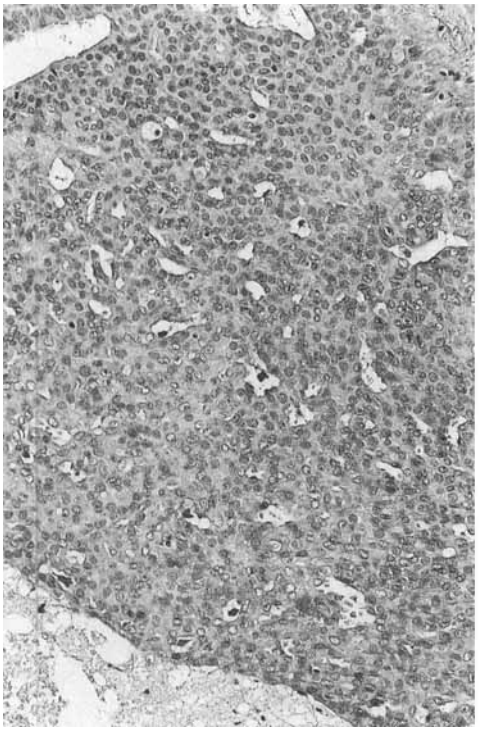

Fig. 2. Usual hyperplasia. Note irregular cell placement, cytological variability, and irregular slit-like spaces.

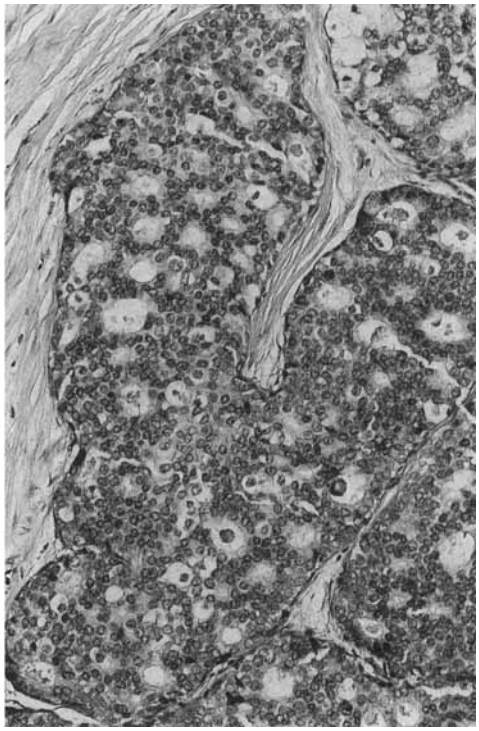

Fig. 3. Ductal carcinoma *in situ*. Note uniform nuclear features, regularly spaced placement of cells, and sharply punched-out holes.

tion of evenly spaced cells with atypical nuclear features present throughout at least two involved spaces with no other cell population present. In addition, the spaces formed by the neoplastic cells must be well rounded with a punched-out, almost cookie cutter appearance (Fig. 3). Alternatively, the neoplastic cells must form bulbous papillary fronds. Unlike usual hyperplasia, the cells present in DCIS generally have distinct cell borders with rounded, uniform-appearing nuclei, similar to one another both in appearance and in relative placement to each other. Tavassoli and Norris [16] have added the requirement that the entire lesion be at least 2 mm in aggregate diameter to qualify as DCIS. We believe this is a useful adjunct to diagnosis, but it simply restates the two space rule.

If a lesion fails to meet all these criteria, but exhibits some of them, then it is properly diagnosed as atypical ductal hyperplasia. Most frequently, a lesion suspicious for DCIS will fail to completely involve the space in which it is present, and a second obviously different population of cells will also be evident.

The relative risk of subsequently developing invasive breast cancer following diagnosis of small, non-comedo DCIS is approximately 10-fold greater than in control populations of women. This translates into an absolute risk of about 25% over the next 10–15 years of the woman's life. In the absence of family history, the relative risk for atypical ductal hyperplasia is approximately 4-fold, and the absolute risk approaches 10% over the same time period. For women with atypical ductal hyperplasia and a positive family history, the relative and absolute risks closely approximate those of DCIS. One important point is that while the risk implications for atypical ductal hyperplasia are bilateral, the diagnosis of DCIS predicts the development of an invasive carcinoma in the same breast in which the original biopsy was performed.

ATYPICAL LOBULAR HYPERPLASIA AND LOBULAR CARCINOMA *IN SITU*

In contrast to ductal lesions, whose marked variability in histologic presentation leads to

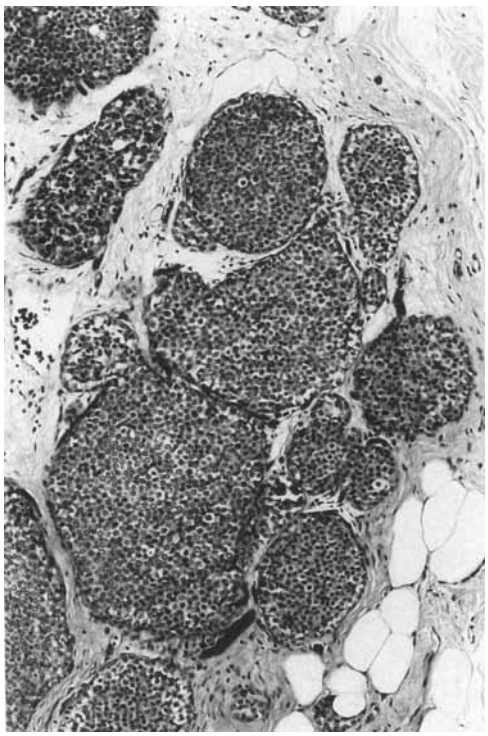

Fig. 4. Lobular carcinoma *in situ*. Complete filling of acini by uniform cells of lobular neoplasia is evident, along with distention of greater than 50% of the acini.

many potential pitfalls in diagnosis, the lesions comprising lobular neoplasia (atypical lobular hyperplasia and LCIS) are much simpler to conceptualize and categorize. For LCIS, a diagnosis is made when all acini present within a lobular unit are filled with a pure and cytologically characteristic population of lobular neoplasia cells, and more than half of the acini of the lobular unit are expanded and distorted (Fig. 4). Whenever less than 50% of acini are distended and distorted, or when all acini are not filled by lobular neoplasia cells, the diagnosis is atypical lobular hyperplasia. The risk implications for these diagnoses are quite similar to the analogous ductal lesions, therefore the relative risk of atypical lobular hyperplasia is 4-fold greater than that of control populations, and the risk of LCIS is 10-fold greater. Both of these diagnoses appear to represent markers of increased risk, because both predict an increased invasive breast cancer risk in either breast.

CONCLUSIONS

In summary, carefully performed epidemiological studies of large cohorts of women with benign breast biopsies have greatly contributed to our ability to provide breast cancer risk assessments to women with specifically defined histological alterations of the breast. The usefulness and reproducibility of this approach has been verified by several recent studies that have produced a general consensus in regards to diagnostic criteria and the level of attendant risk for specific histological lesions. Thus far, histology remains the only widely accepted and verified method of morphological assessment of breast tissue with regard to subsequent breast cancer risk. Although fine needle aspiration cytology is a useful means of diagnosing invasive breast cancer, at present it cannot reliably diagnose premalignant breast disease.

In addition to identifying several general markers of increased risk, epidemiological studies have identified DCIS as a non-obligate precursor lesion that may represent the final stage of premalignancy prior to the development of an invasive breast carcinoma. Because of this unique status, it is our opinion that a major effort should be focused on the molecular alterations responsible for this disease, as these changes may represent the most fundamental modifications leading to the development of invasive breast cancer. Once these changes (which presumably would represent molecularly defined intermediate endpoints) are identified, it is reasonable to assume that fine needle aspiration could play an important role in breast cancer risk evaluation by providing tissue to screen for these alterations, either by immunoperoxidase staining or polymerase chain reaction-based methods.

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