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Clinical and Histologic Aspects of Proliferative and Non-Proliferative Benign Breast Disease

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Abstract It has been known for years that benign breast disease is correlated with an increased risk for the development of breast cancer. Over the years, there have been many studies linking histological changes in benign breast biopsies and subsequent risk of breast cancer. In many of these reports, there was no attempt to standardize criteria and often the patient population under study was relatively small. Over the past decade, three large groups have agreed to use the same definition of benign changes and a unified set of criteria for the diagnosis of these lesions. The results from these three groups [Nashville, Nurses Health Study (NHS), and the Breast Cancer Detection Demonstration Project (BCDDP)] are strikingly similar. All three studies reported that if the biopsy revealed proliferative disease without atypia, the subsequent risk was ~1.5×. If the biopsy revealed atypical hyperplasia (AH), the risk was ~4–5×. If the patients with AH had a family history of breast cancer, their subsequent risk approached that of patients with *in situ* carcinoma (~8–10×). In addition to family history, menopausal status seemed to play a role. In patients with AH, the breast cancer risk was much higher in pre- than post-menopausal patients.

While the classification scheme proposed by Page and co-workers is useful in assigning different levels of risk to women with benign breast disease, it has not been universally accepted. Our major short-term goal should be to encourage pathologists to apply these criteria in a reproducible manner in their daily practice. Our long-term goals should first include a refining of the criteria for AH, especially atypical ductal hyperplasia. A second important area for future study is to further analyze the interaction between histological, biological, and epidemiological factors (such as family history, menopausal status, exogenous hormone use, and dietary factors) on subsequent breast cancer risk. Accomplishing these goals will require a combination of careful histopathological evaluation and application of new biological markers to breast specimens from women in large cohorts with long-term follow-up.

Key words: Atypical hyperplasia, benign breast disease, breast cancer

For decades, pathologists have realized that benign areas in breasts removed for cancer often showed more proliferation and atypia than benign breast tissue from women without cancer [1]. This observation led to numerous retrospective studies evaluating changes in benign biopsies and subsequent cancer risk [2–5]. In these studies, patient populations were often small and various definitions of atypia were used. For these reasons, it was difficult to generalize the results, and the clinical utility of the information derived from these studies was limited.

In 1985, Dupont and Page [6] published the results of a long-term retrospective cohort follow-up study of over 3000 Nashville women who had benign biopsies. That study indicated that the risk of subsequent breast cancer is not significantly increased for women with non-pro-

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liferative changes, moderately increased for women with proliferative changes without atypia, and substantially increased for women with atypical hyperplasia of either the ductal or lobular types. Based on the size of this study [7] and the relatively well-defined categories of breast changes, these findings could be clinically useful in approaching women with benign breast changes or "disease." The National Cancer Institute (NCI) funded a number of studies to determine whether other pathologists working with different patient populations could reproducibly apply Page's criteria. To date, the results of two large, population-based, retrospective cohort studies utilizing Page's criteria have been published [8,9]. In these studies, experienced breast pathologists standardized their criteria with those of Dr. Page before beginning the histologic review. The two groups are the Nurses' Health Study (NHS) [8] and the Breast Cancer Detection Demonstration Project (BCDDP) [9] (Table I). This paper will summarize the results of these three studies.

TABLE I. The Number of Eligible Women and the Number of Women With Evaluable Benign Biopsies Who Subsequently Developed Breast Cancer (Cases) From Three Series

	Nashville	NHS	BCDDP
Cases	134	121	95
Controls		488	190
Total Population	3303	121,700	>280,000

NHS = Nurses Health Study
BCDDP = Breast Cancer Detection Demonstration Project

In all three studies, the pathologists were blinded with regard to patient outcome. Benign biopsies were classified into three broad categories: (1) *non-proliferative changes* including normal breast tissue, cysts, apocrine metaplasia, and mild ductal hyperplasia; (2) *proliferative changes (or disease) without atypia* including papillomas, sclerosing adenosis, fibroadenoma, and moderate to florid ductal hyperplasia of the usual type; and (3) *atypical hyperplasia of either ductal or lobular types*. In these studies, atypical hyperplasias were defined as epithelial proliferations with some features of ordinary hyperplasia and some features of carcinoma *in situ* [7].

The results of these three studies are remarkably similar despite differences in study design and patient populations. In all three studies there was a slightly elevated relative risk of subsequent breast cancer for patients with proliferative changes without atypia (~1.5×), and a substantially increased risk when the biopsy revealed atypical hyperplasia (4–5×) when compared with women with non-proliferative changes (Table II).

Additional factors, such as family history and menopausal status, were also found to influence the subsequent cancer risk for patients in these studies. A positive family history of breast cancer in a first-degree relative slightly increased the risk of subsequent breast cancer in women with proliferative changes without atypia (2.6–4.5×) and markedly increased the risk in patients with atypical hyperplasia (7.3–22×) (Table III). Two studies evaluated menopausal status as a risk

TABLE II. Relative Risk of Breast Cancer According to Histologic Subtype of Benign Breast Biopsy

	Non-proliferative	PWA	AH
Nashville	1	1.9 (1.6–2.3)	5.3 (3.1–8.8)
NHS	1	1.6 (1.0–2.5)	3.7 (2.1–6.8)
BCDDP	1	1.6 (0.77–2.2)	4.3 (1.7–11)

PWA = Proliferative change of "disease" without atypia;
AH = Atypical hyperplasia of the ductal or lobular type.
Numbers in parentheses represent 95% confidence intervals.

TABLE III. Effect of Family History of Breast Cancer in First-Degree Relative (+FH) on the Relative Risks of Breast Cancer According to Histologic Subtype of Benign Biopsy

	Non-proliferative	PWA +FH	AH +FH
Nashville	1	2.7 (1.4–5.3)	8.9 (2.6–27)
NHS	1	4.5 (1.1–18.4)	7.3 (1.1–50.1)
BCDDP	1	2.6 (1.0–6.4)	22.0 (2.4–203)

PWA = Proliferative change or "disease" without atypia;
AH = Atypical hyperplasia of the ductal or lobular type.
Numbers in parentheses represent 95% confidence intervals.

factor, and both studies found it to be an important modulator of risk. In particular, the relative risk of breast cancer among women with atypical hyperplasia was greater in premenopausal (5.9–12×) than postmenopausal women (2.3–3.3×) (Table IV) [8–9].

The risk of subsequent breast cancers in patients with both atypical ductal and atypical lobular hyperplasia was approximately equal in both breasts [10]. This observation was not unexpected for patients with atypical lobular hyperplasia, since the closely related lesion, lobular carcinoma *in situ*, is also associated with a bilaterally increased risk [11,12]. That atypical ductal hyperplasia is also associated with bilaterally increased risk was somewhat surprising, given that it has some morphological similarities to noncomedo ductal carcinoma *in situ*, which is associated with unilaterally increased risk [13–15].

A number of controversies remain concerning the clinical applicability of the diagnosis of atypical hyperplasia [16,17]. It is clear that if pathologists use histological criteria for atypical hyperplasia that are different from those used in the three studies summarized here, the diagnosis of atypical hyperplasias may not carry the same relative risk for subsequent breast cancer seen in these studies [18–20]. As was aptly demonstrated by Dr. Rosai [20], if one does not use a standardized set of criteria for diagnosing borderline breast lesions, the interobserver concordance will be unacceptably low. This interobserver variability can be substantially improved by using standardized criteria and pathologist education [21].

In conclusion, women whose biopsies show proliferative changes without atypia have a slightly elevated relative risk of developing breast cancer. This risk is increased substantially if the biopsy reveals atypical hyperplasia. A history of breast cancer in a first-degree relative increases the risk slightly in women with proliferative changes without atypia and markedly in women with atypical hyperplasia. The elevated risk in women with atypical hyperplasia appears to decrease after menopause. The increased risk is seen bilaterally for both atypical ductal and lobular lesions.

TABLE IV. Effect of Menopausal Status on Relative Risk of Breast Cancer in Patients With Atypical Hyperplasia

	Premenopausal	Postmenopausal
NHS	5.9 (2.6–13.2)	2.3 (0.9–5.9)
BCDDP	12.0 (2.0–68.0)	3.3 (1.1–10.0)

Numbers in parentheses represent 95% confidence intervals.

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