Benign Breast Disease and Breast Cancer Risk: Potential Role for Antiestrogens

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Abstract
Evidence from clinical follow-up studies has indicated that there is a relationship between the presence of histologically proven benign breast disease and breast cancer risk, and that the risk varies according to the histological category of benign breast disease and hormonal status. The risk associated with these histological factors appears to be equal in both breasts, suggesting that these factors are best considered markers of generalized increased breast cancer risk rather than direct precursor lesions. A number of interesting observations gleaned from the Nashville Study, the Breast Cancer Detection Demonstration Project and the Nurses’ Health Study, among other studies, provide evidence of an interaction between these histological risk factors and estrogen in determining the level of breast cancer risk. In the National Surgical Adjuvant Breast Project P-1 trial, tamoxifen was associated with an 86% reduction in breast cancer risk among a small subset of women with biopsy-proven atypical hyperplasia. Taken together, these observations strongly suggest that there is an interaction between estrogen and histological factors in determining breast cancer risk, and that it may be possible to reduce the risk associated with these histological risk factors using antiestrogen therapy.

Introduction
A relationship between certain types of benign breast disease and breast cancer risk has long been recognized. Two types of studies have evaluated this relationship. In the first type, the prevalence of benign alterations in breasts with cancer were compared with their prevalence in breasts without cancer (1, 2). Whereas these studies demonstrated that some benign lesions are more common in cancer-containing breasts than in breasts without cancer, the histological coexistence of certain benign breast lesions with breast cancer is not sufficient to establish that those benign lesions impart an increased cancer risk. More recent studies have evaluated the subsequent risk of developing breast cancer in patients who have had a benign breast biopsy and for whom long-term follow-up is available (3–13). In these studies, the benign biopsies were reviewed, and the types of benign lesions present were recorded and related to the risk of breast cancer. In some of these studies, it was also possible to study the interaction of the histological findings with various clinical and epidemiological factors. Evidence from these clinical follow-up studies has indicated that there is a relationship between the presence of histologically proven benign breast disease and breast cancer risk, that the level of risk varies according to the histological category of benign breast disease, and that the risk associated with these various histological categories is modified by other factors.

In particular, data from the retrospective cohort study of Dupont, Page, and colleagues from Nashville (4, 14), the nested case-control studies of the BCDDP (Ref. 11), and the Nurses’ Health Study (8, 13) have shown that women who have a benign breast biopsy containing proliferative lesions without atypia have a 1.5- to 2-fold risk of subsequent breast cancer, and that those with a benign breast biopsy exhibiting atypical hyperplasia have a 4- to 5-fold risk of subsequent breast cancer (Table 1). The consistency of the findings among these three studies is related in large part to the fact that the pathologists involved in the review of the benign breast biopsies in these studies all used the same histological criteria to categorize these lesions (15). Because atypical hyperplasias are the benign breast lesions associated with the greatest level of breast cancer risk, a more detailed consideration of these lesions is in order.

Atypical Hyperplasias. Atypical hyperplasias are proliferative lesions of the breast which possess some, but not all, of the features of carcinoma in situ (4, 14, 16) and are categorized as either ductal or lobular in type. Atypical ductal hyperplasias have some of the architectural and cytological features of low-grade ductal carcinoma in situ, such as nuclear monomorphism, regular cell placement, and round regular spaces in at least part of the involved space. Atypical lobular hyperplasias are characterized by changes similar to those of lobular carcinoma in situ but lack the complete criteria for that diagnosis. In addition to involving lobular units, the cells of atypical lobular hyperplasia may also involve ducts (17).

It is important to note that with the increasing use of mammographic screening, atypical hyperplasias are being diagnosed more frequently than in the past. For example, when a biopsy is performed because of a palpable mass, atypical hyperplasia is seen in only about 2–4% of cases (4, 18). In contrast, atypical hyperplasia was identified in 12–17% of biopsies performed because of the presence of mammographic microcalcifications (19, 20).

Clinical follow-up studies have shown that the risk of breast cancer in patients with atypical hyperplasia (of both

1 Presented at the First International Conference on Recent Advances and Future Directions in Endocrine Therapy for Breast Cancer, June 21–23, 2001, Cambridge, MA.
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3 The abbreviations used are: BCDDP, Breast Cancer Detection Demonstration Project; CI, confidence interval.
ductal and lobular types) is approximately equal in both breasts (21). This suggests that atypical hyperplasias are best considered markers of generalized increased breast cancer risk and that risk reduction strategies in these patients need to be directed to both breasts.

Additional evidence that atypical hyperplasias are best viewed as markers of generalized risk is provided by a recent study of the pathology of breast cancers in women with prior biopsy-proven benign breast disease (22). In that study, the histological features of breast cancers in women with a prior biopsy showing nonproliferative lesions, proliferative lesions without atypia, and atypical hyperplasia were compared. Of note, the cancers in the three benign breast disease groups did not differ with regard to tumor size, nodal status, histological type, histological grade, lymphatic vessel invasion, extensive intraductal component, or hormone receptor status. Therefore, the pathological features of breast cancers that develop in women with a prior benign breast biopsy do not appear to vary according to the histological category of the previous benign breast disease, which argues in favor of these benign lesions representing risk indicators rather than direct precursors.

**Interactions between Histological Risk Factors and Hormonal Factors.** A number of interesting observations provide evidence of an interaction between these histological risk factors (particularly atypical hyperplasias) and estrogen in determining the level of breast cancer risk. For example, in the Nashville study, the breast cancer risk associated with atypical hyperplasia decreased with the time following the benign breast biopsy and was substantially higher in the first 10 years after the benign biopsy than after 10 years (23). In that study, the relative risk of breast cancer associated with atypical hyperplasia was 9.8 during the first 10 years following breast biopsy. However, after 10 years, the relative risk decreased to 3.6 ($P = 0.06$). Although this study does not provide direct evidence of an association between menopausal status and breast cancer risk in women with atypical hyperplasia, these findings suggest that as women age and become postmenopausal, the risk associated with atypical hyperplasia decreases.

More direct evidence of an interaction between histological findings and hormonal status is provided by findings from the BCDDP study and the Nurses’ Health Study. Data from the BCDDP study have indicated that breast cancer risk is higher among women with a premenopausal diagnosis of atypical hyperplasia than in women in whom the diagnosis is made post-menopause (11). In that study, women with a premenopausal diagnosis of atypical hyperplasia had a relative risk of breast cancer of 12 (95% CI, 2.0–68), whereas in women with a postmenopausal diagnosis of atypical hyperplasia, the relative risk was only 3.3 (95% CI, 1.1–10). In the Nurses’ Health Study, the presence of atypical hyperplasia in a benign breast biopsy was more strongly associated with premenopausal than with postmenopausal breast cancer (8, 13). In that study, among women with atypical hyperplasia the relative risk of premenopausal breast cancer was 4.6 (95% CI, 2.1–10.4), whereas the risk of postmenopausal breast cancer was 2.6 (95% CI, 1.2–5.6).

Additional evidence of an interaction between atypical hyperplasia and estrogen has been provided by the National Surgical Adjuvant Breast Project P-1 trial. In that study, among women with biopsy-proven atypical hyperplasia, tamoxifen was associated with an 86% reduction in breast cancer risk (24). Although all of these analyses are limited by small sample numbers and, in some instances, broad 95% CIs, taken together, they strongly suggest that there is an interaction between estrogen and atypical hyperplasia in determining breast cancer risk and that it is possible to reduce the risk associated with atypical hyperplasia by using antiestrogen therapy.

Given the foregoing observations, it would be logical to conclude that hormone replacement therapy might increase the risk of breast cancer in postmenopausal women with atypical hyperplasia and might, therefore, be contraindicated in such patients. However, data from both the Nashville study and the Nurses’ Health Study have found no evidence that either past or current use of hormone replacement therapy adds to the risk associated with atypical hyperplasia (or with any other category of biopsy-proven benign breast disease; Refs. 25 and 26). There are several possible explanations for this apparently paradoxical observation. The first is related to patient selection for hormone replacement therapy. It is possible that those women who are most likely to have menopausal symptoms severe enough to require hormone replacement therapy are those with the lowest postmenopausal endogenous hormone levels, and that in these women, the replacement hormones are not associated with sufficient high serum or tissue levels of estrogen to provide a trophic effect on these breast lesions. Another possibility is that in at least some postmenopausal women with atypical hyperplasia, the lesions have lost their sensitivity and/or responsiveness to estrogen and are, therefore, unaffected by hormone replacement. Thus, although it seems counterintuitive to recommend the use of hormone replacement therapy in women with a prior diagnosis of atypical hyperplasia, there are currently no data to support the notion that such therapy should be withheld from these patients if they have menopausal symptoms that are severe enough to otherwise warrant this therapy.

**The Role of Estrogen Receptor.** There is considerable interest in the role of estrogen receptors as a determinant of breast cancer risk in women with benign breast biopsies, but few

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### Table 1

Relative risk of breast cancer according to histologic category of benign breast disease in studies using the criteria of Dupont, Page, and Rogers (4, 14, 16)

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Nonproliferative without atypia</th>
<th>Atypical hyperplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nashville (4)</td>
<td>Retrospective cohort</td>
<td>1</td>
<td>1.9 (1.2-3)</td>
</tr>
<tr>
<td>Nurses’ health study (13)</td>
<td>Case-control</td>
<td>1</td>
<td>1.6 (1.2-2.2)</td>
</tr>
<tr>
<td>BCDDP (11)</td>
<td>Case-control</td>
<td>1</td>
<td>1.3 (0.77-2.2)</td>
</tr>
</tbody>
</table>

Ranges in parentheses represent 95% CIs.
studies have addressed this issue. Khan and colleagues (27) studied estrogen receptor expression in benign breast epithelium in breasts with and without cancer. The results of this study indicated that women whose breast tissue contained cancer were three times more likely to have estrogen receptor-positive benign breast epithelium (defined as receptor expression in 1% or more of the benign epithelial cells) than those whose breast tissue did not show cancer. Although this evidence is indirect, it raises the possibility of a positive association between estrogen receptor expression in benign breast tissue and risk of breast cancer. However, this association needs to be evaluated in the setting of a clinical follow-up study.

More recently, Faqua and colleagues (28) have identified a mutation in the estrogen receptor-α gene in about one-third of cases of ductal hyperplasia without atypia. In vitro, this mutation is associated with an increased sensitivity to the effects of estrogen. It is possible that ductal hyperplasias harboring this mutation may be hypersensitive to the effects of estrogen; this hypersensitivity may confer a proliferative advantage to the cells and provide an environment for the accumulation of additional genetic abnormalities, which, in turn, could result in the development of cancer. Again, clinical follow-up studies will need to determine whether this type of mutation is associated with an increased risk of breast cancer.

Conclusions. The results of clinical follow-up studies have indicated that the level of breast cancer risk in women with biopsy-proven benign breast disease varies according to the histological category of the benign breast disease. In particular, women with atypical hyperplasia are at a substantially increased risk for the development of breast cancer. There appears to be an interaction between atypical hyperplasia and the hormonal milieu in determining the level of breast cancer risk, with the risk of high-grade DCIS being the pathway that we can “prevent”—and the other being a pathway that either escapes very rapidly or bypasses some of these intermediate steps.

Dr. Schnitt: I think that there’s at least two. We usually don’t see ADH in the vicinity of high-grade DCIS. So what is the precursor lesion for high-grade DCIS? Is it normal epithelium? Do some low-grade DCIS lesions get additional hits and then they dedifferentiate so quickly that the low-grade DCIS is obliterated? I think there are possibly three pathways. One is ER positive all along through ADH to low-grade DCIS. One is high-grade DCIS to high-grade invasive cancer with some unknown precursor, and another is a cross-over from the low-grade to the high-grade pathway. But again, I’m sure that’s overly simplistic as well.

Open Discussion

Dr. Kent Osborne: Just looking morphologically at hereditary versus sporadic breast cancer, do you get a sense that hereditary breast cancers evolve according to the classical scheme?

Dr. Schnitt: The reported finding in the literature is that DCIS is less commonly seen in BRCA1-associated breast cancers than with sporadic breast cancers. In a simplistic way, you can hypothesize based on emerging genetic evidence that there are two lines of progression to breast cancer, one that goes through atypical hyperplasia to low-grade DCIS to low-grade invasive cancer, and one that grows from high-grade DCIS to high-grade invasive cancer. Whether one of those pathways can diverge into the other, whether the low-grade lesions can go bad and become high-grade, no one knows. What the precursor lesions are in women with hereditary breast cancer is an unanswered but extremely important question, but it’s also important for sporadic breast cancer as well. Although the numbers were small, in the Nurses’ Health Study we found that the histological features of the breast cancers and the ER status bore absolutely no relationship to the prior category of benign breast disease.

Dr. Matthew Ellis: The morphological progression genetic program is separate from the invasion and metastases programs. They’re a completely distinct set of programs that evolve at different rates, giving rise to this heterogeneity. You see these low-grade cancers with lymph nodes full of metastatic cells, and then you have big high-grade cancers that are restricted to the breast.

Dr. Schnitt: Right, and conversely, you not infrequently see extensive high-grade DCIS lesions with microinvasion.

Dr. Victor Vogel: Are we willing to say at this point that we think there are two pathways, one in which there is ER positivity, hormone dependence, and this pathological progression through atypia and in situ cancer to invasive disease—that being the pathway that we can “prevent”—and the other being a pathway that either escapes very rapidly or bypasses some of these intermediate steps?

Dr. Schnitt: I think that there’s at least those two. We usually don’t see ADH in the vicinity of high-grade DCIS. So what is the precursor lesion for high-grade DCIS? Is it normal epithelium? Do some low-grade DCIS lesions get additional hits and then they dedifferentiate so quickly that the low-grade DCIS is obliterated? I think there are possibly three pathways. One is ER positive all along through ADH to low-grade DCIS. One is high-grade DCIS to high-grade invasive cancer with some unknown precursor, and another is a cross-over from the low-grade to the high-grade pathway. But again, I’m sure that’s overly simplistic as well.

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