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RISK AND PREVENTION (ME WOOD, SECTION EDITOR)

Breast Atypia as a Biomarker of Risk

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Abstract
Purpose of Review Provide a summary of available evidence on breast atypia as a biomarker of risk.
Recent Findings With an increase in independent studies on atypical hyperplasia (AH), knowledge has advanced recently regarding its subsequent associated breast cancer risk. For women with AH, absolute risk can be estimated generally as ~ 1% per year, and a greater extent of disease appears to further increase risk. Although both breasts are at increased risk, the risk is higher for the ipsilateral breast. In women with AH, a family history of breast cancer does not confer significantly increased risk. Risk is similar for atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH), with some reports suggesting mildly higher risk for ALH. Prevention medications reduce breast cancer risk by ~ 70% in AH.
Summary Women with AH should be counseled on their increased risk and the option of prevention medication.

Keywords Atypical hyperplasia · Breast · Risk · Risk prediction · Breast cancer · Biomarker

Introduction

Atypia of the breast usually refers to a histologic diagnosis of atypical hyperplasia, although strictly speaking the word "atypia" is a general histopathologic term used to describe phenotypically abnormal cytologic changes in epithelial cells. Atypical appearing epithelial cells can be present in many breast lesions, such as papilloma with atypia, radial scar with atypia, or flat epithelial atypia, in addition to the two distinct entities of atypical hyperplasia (AH): either atypical lobular hyperplasia (ALH) or atypical ductal hyperplasia (ADH). Although this distinction between the word "atypia" and the diagnosis of "atypical hyperplasia" may appear semantic, it is a clinically important distinction because a diagnosis of AH indicates an increased risk for future breast cancer whereas isolated cytologic atypia does not. This article will review the evidence supporting atypical hyperplasia as a biomarker of future breast cancer risk, with a focus on important recent findings and controversial aspects.

The association of breast cancer risk and AH was reported in the 1985 landmark paper of Dupont and Page [1]. This study described breast cancer risk in the Nashville Breast Cohort, a cohort of 10,366 women who had undergone benign breast biopsy and who were evaluated for later breast cancer events. The main finding was that breast cancer risk differed in women depending on the histologic findings in their benign breast biopsy. Breast cancer risk was highest in the women whose biopsies demonstrated AH, with a fivefold increased relative risk of breast cancer compared with that in the general population. This paper raised awareness of the long-term risk of breast cancer associated with AH and provided the histopathologic definition of AH that was clarified in 1992 [2] and is still used today.

Since then, multiple studies have corroborated the increased breast cancer risk associated with AH. Among earlier studies, the Breast Cancer Demonstration and Detection Project reported a relative risk of 3.0 [3], the Nurses' Health Study reported a relative risk of 3.7 [4], and the Mayo Benign Breast Disease Cohort Study reported a relative risk of 4.2 [5]. More recent reports on atypical hyperplasia and breast cancer risk have addressed issues of absolute risk and potential factors modifying risk among women with atypical hyperplasia.

Atypical Hyperplasia as a Biomarker for Absolute Risk of Breast Cancer

Early reports documented the increased *relative* risk of breast cancer after a diagnosis of AH. While an important and critical step in

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counseling women about risk, the relative risk data was somewhat difficult for clinicians and patients to comprehend for patient decision-making. More recent reports have provided estimates of *absolute* breast cancer risk associated with atypical hyperplasia. In the Mayo Benign Breast Disease Cohort Study of ~ 9000 women initially reported in 2005, relative risk of breast cancer was 4.2 among the 336 women with AH, similar to the Nashville Cohort [5]. After the expansion of the cohort to ~ 13,000 women, long-term follow-up of 698 women with AH demonstrated a steady and sustained increase in breast cancer risk extending beyond 20 years, with an average absolute risk of ~ 1% per year [6]. More recently, data from two other cohorts shows slightly higher annual absolute risk of breast cancer in women with AH. The Partners Cohort includes 2938 women with high-risk lesions from 1987 to 2010 including lobular carcinoma in situ (LCIS), ALH, ADH, or severe ADH [7]. Among the 713 women with ADH and 488 with ALH who did not receive any prevention therapy, average annual absolute risk was 1.7% in ADH and 2.1% with ALH. Additional recently published data comes from the Cleveland Clinic Cohort, with 212 women with AH from 1995 to 2010 (including some with LCIS) [8•]. In this group, < 15% took prevention medications. With a median follow-up of 7.3 years, absolute risk of breast cancer averaged per year was 1.4%.

Some investigators have appropriately questioned whether breast cancer risk associated with AH varies depending on the technique of biopsy. In 2017, Menes et al. published data from the Breast Cancer Screening Consortium (BCSC), suggesting that breast cancer risk is lower in more modern screened cohorts of ADH specifically that was diagnosed percutaneously compared with that in the early cohorts of patients diagnosed by surgical excisions [9•]. In the early reports, AH was indeed diagnosed in breast tissue from surgical excisional biopsies [1, 5, 4]. In the BCSC study, Menes et al. evaluated breast cancer events in 1727 women with ADH diagnosed from 1994 to 2011, with 61% diagnosed by percutaneous needle biopsy [9•]. They reported a 10-year absolute risk of 5.7% for invasive breast cancer events, which averages to an annual risk of ~ 0.6% that is lower than the absolute risk estimates from the other cohort studies. Furthermore, the 10-year risk was lower among the women diagnosed percutaneously (5.0%, 95% CI 2.2–8.9) compared with those diagnosed by surgical excision (6.7%, 95% CI 3.0–12.8), but this was not statistically significant. In the recent Partners and Cleveland Clinic Cohorts, percutaneous needle biopsy was also common (~ 60% of the biopsies in the Partners Cohort and 100% of the biopsies in the Cleveland Clinic Cohort) and the risk was > 1% per year in both of these cohort studies, suggesting that biopsy technique does not account for the differences in reported absolute risk. Importantly, the BCSC study included *only invasive* breast cancers in their endpoint, whereas ductal carcinoma in situ (DCIS) was included as a breast cancer event in the other cohort studies. With DCIS generally constituting ~ 20% of breast cancers, the exclusion of DCIS events accounts at least partially for the lower estimates of BC risk in the BCSC study. More intensive follow-up methods may also account for a higher frequency of detected events in the cohort studies compared with those of the BCSC study. Therefore, the preponderance of the data from all the available evidence indicates that for a woman with atypical hyperplasia, her risk of breast cancer averages ~ 1% per year.

Other Factors Modifying Risk in Women with Atypical Hyperplasia

As clinical care moves toward increased efforts to personalize care, it is desirable to identify factors that may further refine risk estimates for an individual woman. Unfortunately, standard clinical risk models (Gail model and Tyrer-Cuzick model) do not predict individual risk well for women with AH (c-statistics of 0.50–0.54) [10, 11], driving efforts to find additional features that stratify risk and to develop clinical risk prediction models for women with AH.

Risk in ADH Versus ALH

An early factor investigated for its impact on risk was the histologic subtype of atypical hyperplasia, i.e., ADH versus ALH, with differing results across various studies. In 1985, data from the Nashville Breast Cohort showed similar risk for ADH (RR 4.3) and ALH (RR 4.2) [12]. In contrast, the Nurses' Health Study has reported higher risk for ALH (OR 5.3) compared with that for ADH (OR 2.4) [13]. This difference has persisted with longer term follow-up reported by their group in 2007 [14] and 2016 (OR 6.6 for ALH versus OR 3.2 for ADH) [15••]. In the Mayo Benign Breast Disease Cohort, the risk appears slightly higher for ALH than for ADH, but this difference is not statistically significant and 95% confidence intervals were similar (RR of 4.76 (3.74, 5.97) for ALH and RR 3.93 (3.00, 5.06) for ADH) [6]. In the Partners Cohort, breast cancer risk associated with ADH was lower than for ALH and LCIS at the 5-year time point, but the risk was similar for both by the 10-year time point [7]. A separate meta-analysis of four case-control studies identified higher risk associated with ALH (OR 5.14, 95% CI 3.5–7.5) compared with ADH (OR 2.9, 95% CI 2.2–4.0) [16]. In summary, this point remains controversial, with some data supporting a greater risk associated with ALH, and some data indicating no significant difference in risk for women with ADH versus those with ALH.

Family History and Risk in AH

Due to the longstanding knowledge that a family history of breast cancer impacts risk, family history was evaluated early as a possible factor impacting risk in women with AH. In their seminal report on the Nashville Cohort, Dupont and Page reported a

higher risk of breast cancer in the 39 women with both AH and a family history of breast cancer (RR 8.9, 95% CI 4.8–17) compared with that in the 193 women with AH but no family history (RR 3.5, 95% CI 2.3–5.5) [1]. In contrast, the Nurses' Health Study found no difference in risk based on family history [17], nor did the Mayo Benign Breast Disease Study when comparing a much larger number of women with AH and a family history ($n = 257$) versus no family history ($n = 327$) [18]. In addition, the meta-analysis of case-control studies showed that a first-degree family history did not increase risk in women with AH (OR 1.39, 95% CI 0.82–2.37, $p = 0.53$) [16]. Therefore, the preponderance of data indicates that family history probably does not increase risk further in women diagnosed with AH.

Laterality of Risk

Data are consistent across multiple studies on two main points regarding AH and the laterality of later breast cancer. First, breast cancer risk is elevated for both breasts after a diagnosis of AH, as the later breast cancers do not all occur within that breast. However, there is a predilection for subsequent ipsilateral cancer, with 56–68% of later cancers occurring in the breast that underwent biopsy demonstrating AH [19, 14, 6]. This pattern of increased ipsilateral risk has been observed for both ALH and ADH. In the Mayo Benign Breast Disease Cohort, this was further evaluated regarding time to later breast cancer. Although ipsilateral breast cancers were more likely at all 5-year intervals up to 20 years, there was an early ipsilateral predominance. Within the first 5 years after biopsy, 80% of cancers occurred in the ipsilateral breast, whereas only 62% of cancers developing more than 5 years after biopsy were ipsilateral ($p = 0.04$) [6].

Extent of AH and Risk

In 1991, Page et al. reported higher breast cancer risk in women with LCIS compared with those with ALH, suggesting that the extent of disease along the spectrum of lobular neoplasia impacts breast cancer risk [20]. In 2007, Degnim et al. reported that the number of foci of AH significantly stratified subsequent breast cancer risk [21]. This finding was confirmed in a later report on the expanded cohort of 698 women with AH, with relative risks of 3.2, 5.5, and 7.6 for 1, 2, and ≥ 3 foci of AH, respectively [6]. A subsequent report demonstrated that the number of foci of AH stratified risk significantly in both subtypes of AH in the Mayo Cohort, with relative risks of 2.6, 5.2, and 6.4 for 1, 2, and ≥ 3 foci respectively for ADH, and relative risks of 2.6, 3.5, and 6.8 for 1, 2, and ≥ 3 foci respectively for ALH [22]. Findings were similar in the Nashville Cohort, where the risk increased significantly for ADH (RRs of 2.7, 5.2, and 15.1 for 1, 2, and ≥ 3 foci, respectively) but not for ALH (RRs of 2.6, 3.5, and 4.0 for 1, 2, and ≥ 3 foci, respectively). The number of foci of AH is one of two key variables in a risk model developed from the Mayo Cohort (the AH-BC model) to estimate breast cancer risk specifically in women with AH (the other variable is age) [23••]. For the prediction of breast cancer events at 10 years, the model demonstrated good discrimination (c-statistic 0.63) and calibration (0.87), and the model validated with slightly less discrimination in the Nashville Cohort (0.59) [23••].

In contrast to these findings in the Mayo and Nashville Cohorts, greater extent of AH did not correlate with significant increases in breast cancer risk in the Nurses' Health Study [15••]. In women with ADH, risk was no higher for 3+ foci (OR 2.7) compared with those with 1 or 2 foci (OR 3.5). In women with ALH, risk appeared higher in women with 3+ foci (OR 8.0) versus 1 or 2 foci (OR 5.2), but the difference was not statistically significant. Reconciling the contradictory findings on this issue is challenging and important. Although somewhat tangential, it is interesting to note that an independent study of LCIS also found that increased extent of disease (assessed as > 50% of biopsy slides) was associated with increased risk of breast cancer [24]. Therefore, it is biologically plausible that a greater extent or burden of high-risk lobules within the breast correlates with a higher risk of developing breast cancer. Some possible reasons for the different findings in the Nurses' Health Study are incomplete procurement of biopsy materials for review and the nested case-control design (versus the cohort approach in the Mayo and Nashville studies) [25••].

Novel Biomarkers for Refining Risk in Atypical Hyperplasia

Ongoing research has investigated additional novel biomarkers that may help to further stratify risk in women with AH. Ki67 is a biomarker of cell proliferation in breast cancer that is prognostic of outcome and response to hormonal therapy and [26] that has also been evaluated in AH. In a sample of 192 women with AH, Ki67 was a time-dependent biomarker of risk [27]. The percentage of Ki67-positive cells was quantitated with digital histology methods within the atypical hyperplasia lesion. For women with AH and Ki67 ≥ 2%, risk was increased in the first 10 years after AH diagnosis, whereas for women with AH and Ki67 < 2%, risk was not increased significantly until after 10 years of follow-up [27]. Estrogen receptor beta (ERbeta) is another potential biomarker of interest in AH. ERbeta demonstrates tumor suppressor function. In a study of 171 women with AH in the Mayo Benign Breast Disease Cohort, ERbeta expression by immunohistochemistry was quantified in both AH and normal background lobules [28]. ERbeta expression was lower in the AH compared with that in normal lobules, and higher ERbeta expression in either AH or normal lobules was associated with an approximate twofold decreased risk of breast cancer [28]. Cyclooxygenase-2 (COX2) is another biomarker that has been

evaluated as a stratifying biomarker in women with AH. Inflammation is increasingly recognized as important in carcinogenesis, and COX2 has a protumorigenic role in preclinical models [29]. COX2 expression was evaluated with immunohistochemistry in 235 women with AH and was categorized as negative, weak, moderate, or strong. Subsequent breast cancer risk was higher with increasing COX2 expression (RR 2.63 negative or weak, RR 3.56 moderate, and RR 5.66 strong), although not statistically significant ($p = 0.07$) [30]. While these biomarker studies are promising, further validation is needed prior to clinical use. In addition to these proposed biomarkers of risk in AH, other efforts have focused on biomarker discovery in normal breast tissues [31] or in AH adjacent to cancer [32], as alternate strategies for biomarker identification. To date, none of these novel breast tissue biomarkers in AH have been validated for clinical use.

Summary

Women with AH have an approximate fourfold increased risk of breast cancer, and recent data from multiple sources indicates an absolute risk of ~ 1% per year that persists over the long term. Long-term risk is elevated for both breasts but is higher for the ipsilateral breast. ADH and ALH have similar risk, or risk may be slightly higher for ALH. In women with AH, a family history of breast cancer is not associated with further increases in breast cancer risk. Increasing extent (amount) of AH is associated with greater risk and has been incorporated into a risk prediction model for women with AH. Research is underway to identify additional biomarkers that (when validated) may help to stratify risk more effectively in women with AH.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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