SPECIAL REPORT

Atypical Hyperplasia of the Breast — Risk Assessment and Management Options

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Breast biopsies are commonly performed to evaluate mammographic or palpable findings that are of concern, and the majority reveal benign findings. More than 1 million of the breast biopsies that are performed annually in the United States are found to be benign.[1] On the basis of the histologic findings, it is possible to stratify women with benign biopsy findings into groups with significantly different risks of later breast cancer.[2,3] Atypical hyperplasia is a high-risk benign lesion that is found in approximately 10% of biopsies with benign findings.[4] In this article, we examine these benign lesions because they have special importance as a predictor of future breast cancer. There are two types of atypical hyperplasia, as classified on the basis of microscopic appearance: atypical ductal hyperplasia and atypical lobular hyperplasia; these occur with equal frequency and confer similar risks of later breast cancer (Table 1).[2,3,9,10] Thus, throughout this article, the varieties will be referred to together as "atypical hyperplasia."

In atypical hyperplasia, there is a proliferation of dysplastic, monotonous epithelial-cell populations that include clonal subpopulations.[11] In models of breast carcinogenesis, atypical hyperplasia occupies a transitional zone between benign and malignant disease, because it contains some of, but not all, the requisite features of a cancer and is thus considered to be premalignant.[12-14]

In studies with long-term follow-up, atypical hyperplasia has been shown to confer a relative risk for future breast cancer of 4.[2,3,5,7,9,10] Although these relative-risk statistics have been recognized for decades, only recently has the absolute risk among women with atypical hyperplasia been better characterized, with a cumulative incidence of breast cancer approaching 30% at 25 years of follow-up.[5,15] This high cumulative incidence is not widely recognized, and thus, women with atypical hyperplasia are not included in many high-risk guidelines. For example, screening magnetic resonance imaging (MRI) is not routinely recommended for these women.[16] In addition, studies of the use of chemopreventive agents show that only a small minority of high-risk women take these drugs,[17] despite randomized clinical trials showing substantial benefit specifically for women with atypical hyperplasia.

Because of the high-risk features and high incidence of atypical hyperplasia and the availability of effective breast-cancer prevention strategies, atypical hyperplasia is the benign breast diagnosis that is most important to act on clinically. In this report, we describe the histologic and molecular features of atypical hyperplasia, the current management of the condition, new data on the cumulative risk of breast cancer among women with atypical hyperplasia, current guidelines, and suggestions for more intensive screening and prevention strategies based on accurate risk estimates.

HISTOLOGIC AND MOLECULAR FEATURES

The criteria for the diagnosis of atypical ductal hyperplasia and atypical lobular hyperplasia were established by David Page and colleagues and accepted by the College of American Pathologists in 1985.[9,18] Atypical ductal hyperplasia is characterized by filling and distention of the involved ducts by monotonous epithelial cells forming architecturally complex patterns, including cribriform-like secondary lumens or micropapillary formations (Fig. 1A). In atypical lobular hyperplasia, the acini of a lobular unit are expanded and filled with small, monotonous, round or polygonal cells with a lack of cohesion and a loss of acinar lumens (Fig. 1B). Lobular carcinoma in situ, although histologically similar to atypical lobular hyperplasia, is more ex-

Table 1. Risk of Breast Cancer among Women with Atypical Hyperplasia.*

Study and Study Group	No. of Patients	Standardized Incidence Ratio (95% CI)	P Value
Nashville Breast Cohort, 1985[2]†			
All atypical hyperplasia	232	4.4 (3.1–6.3)	
Family history of breast cancer			
Yes	39	8.9 (4.8–17)	
No	193	3.5 (2.3–5.5)	
Mayo Clinic, 2005, 2014[3,5]‡			
All atypical hyperplasia	698	4.34 (3.66–5.12)	
Type of atypical hyperplasia			0.54
Atypical ductal hyperplasia	300	3.93 (3.00–5.06)	
Atypical lobular hyperplasia	327	4.76 (3.74–5.97)	
Atypical ductal and lobular hyperplasia	32	4.36 (1.75–8.96)	
Age			0.04
<45 yr	100	5.45 (3.17–8.73)	
45–55 yr	233	5.43 (4.13–7.01)	
>55 yr	365	3.54 (2.74–4.49)	
Family history of breast cancer§			0.23
None	372	3.91 (3.05–4.94)	
Weak	151	5.54 (3.94–7.57)	
Strong	106	4.19 (2.68–6.23)	
Foci of atypical hyperplasia			<0.001
1	410	3.19 (2.46–4.07)	
2	161	5.53 (3.95–7.53)	
3	113	7.61 (5.36–10.49)	
Extent of involution			<0.001
None	75	7.66 (4.74–11.72)	
Partial	428	4.63 (3.76–5.65)	
Complete	153	1.91 (1.04–3.20)	
Henry Ford, 2007[6]¶			
Atypical ductal hyperplasia	179	5.0 (2.3–11.0)	
Atypical lobular hyperplasia	67	3.2 (0.83–12.4)	
Nurses' Health Study, 1992[7]‖			
All atypical hyperplasia	74	3.7 (2.1–6.8)	
Menopause status			
Premenopausal	34	5.9 (2.6–13.2)	
Postmenopausal	35	2.3 (0.9–5.9)	
Nurses' Health Study, 2006[8]**			
Family history of breast cancer			0.57
Present	62	5.37 (3.01–9.58)	
Absent	194	4.38 (2.93–6.55)	

* The criteria for inclusion in the table were a central pathological review and the use of the criteria of David Page and colleagues for the diagnosis of atypical hyperplasia.[9] CI denotes confidence interval.

† The study was a retrospective cohort study involving women who had excisional biopsies performed during the period 1950–1968. The median duration of follow-up was 17 years. Risk estimates are for invasive breast cancer only.

‡ The study was a retrospective cohort study involving women who had excisional biopsies, core biopsies, or both performed during the period 1967–2001. The median duration of follow-up was 12.1 years. Risk estimates are for both invasive and in situ breast cancer (19% of cases were in situ). The numbers of patients in subcategories may not add to the total because information was missing for some patients.

§ A strong family history was defined as at least one first-degree relative with breast cancer before 50 years of age or two or more relatives with breast cancer, with at least one being a first-degree relative. A weak family history was defined as any lesser degree of family history.

¶ The study was a retrospective cohort study involving women who had biopsies performed during the period 1981–1994. The duration of follow-up was not specified. Risk estimates are for both invasive and in situ breast cancer (20% of cases were in situ).

‖ The study was a nested case–control study. The type of breast cancer (i.e., invasive or in situ) evaluated for the risk estimates was not specified.

** The study was a nested case–control study; risk estimates are for both invasive and in situ breast cancer.

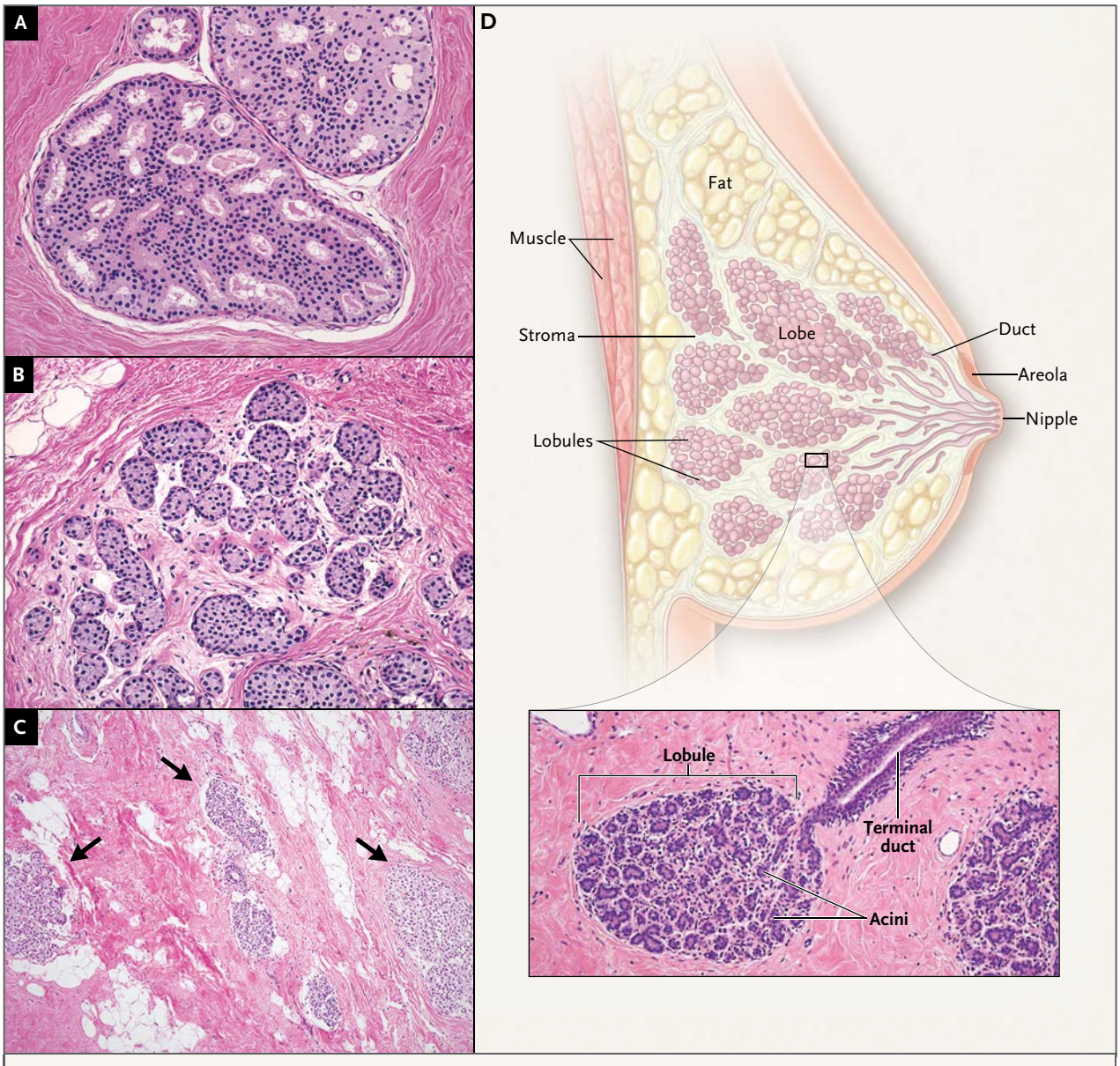

Figure 1. Microanatomical Features of the Breast and Histologic Features of Atypical Hyperplasia.

Panel A shows atypical ductal hyperplasia with a proliferation of monotonous cells in architecturally complex patterns, including secondary lumens and micropapillary formations (reproduced from Hartmann et al.[3]). Panel B shows atypical lobular hyperplasia, with expanded acini filled with monotonous polygonal cells and a loss of acinar lumens. Panel C shows multifocal atypical hyperplasia (in this case, atypical lobular hyperplasia). Atypical lobular hyperplasia is present in more than one terminal duct lobular unit, which are clearly separated from one another by interlobular mammary stroma (arrows). Panel D is an illustration of the microanatomy of the breast, including a photomicrograph of a terminal duct lobular unit.

tensive and is associated with a higher risk of breast cancer (relative risk, 8 to 10).[19,20] Similarly, atypical ductal hyperplasia and low-grade ductal carcinoma in situ share histologic features, but ductal carcinoma in situ is more extensive and is associated with a relative risk of 8 to 10 for later breast cancer.[19,20] Because the difference between carcinoma in situ (either ductal or lobular) and atypical hyperplasia is one of extensiveness of the lesion, some studies have shown a lack of concordance among pathologists in differentiating atypical hyperplasia from

carcinoma in situ.[21] However, other research has shown that when pathologists follow standardized, published criteria, concordance is satisfactory.[22]

Molecular studies have helped define the phenotypic characteristics of atypical hyperplasia. In an early and comprehensive gene-expression study of breast-cancer progression, Ma et al. found similar and progressive transcriptional and epigenetic alterations in specimens of concurrent atypical hyperplasia, carcinoma in situ, and invasive carcinoma, which provided additional evidence for the precursor role of atypical hyperplasia.[23] One distinguishing feature of atypical lobular hyperplasia, lobular carcinoma in situ, and invasive lobular cancer is reduced or absent expression of the cell–cell junction protein E-cadherin. Aberrant expression of E-cadherin can be shown immunohistochemically and is used diagnostically to distinguish between the lobular and ductal phenotypes.[24] In a large study of estrogen-receptor expression in atypical hyperplasia, 97% of atypical ductal hyperplasia lesions and 88% of atypical lobular hyperplasia lesions had estrogen-receptor staining in 10% or more of cells. Of note, both the percentage of positive cells and the staining intensity were greater in ductal lesions than in lobular lesions ($P<0.001$).[25]

RISK

OVERALL RISK FOR ATYPICAL HYPERPLASIA

The landmark longitudinal cohort study describing breast-cancer risk associated with atypical hyperplasia was reported by David Page and William Dupont in 1985.[2] In that study involving 3303 women who had had a breast biopsy with a benign finding (the Nashville Breast Cohort), the authors identified reproducible categories of benign lesions with varying levels of later breast-cancer risk. The cohort included 232 women with atypical hyperplasia; their relative risk for a later invasive breast cancer was 4.4 (95% confidence interval [CI], 3.1 to 6.3).[2] Since the time that report was published, other investigators using either cohort or case–control study designs have shown consistently that the relative risk associated with both atypical ductal hyperplasia and atypical lobular hyperplasia is approximately 4 (Table 1).[3,5-7] More recent data on absolute risk from the Nashville Breast Cohort (unpublished data) and another large cohort at the Mayo Clinic[5] confirm the cumulative high risk of breast cancer among women with atypical hyperplasia. Specifically, 25 years after a biopsy that showed atypical hyperplasia, breast cancer (either in situ or invasive) developed in 30% of the women in the Mayo Clinic cohort (Fig. 2A). Similar updated results were obtained in the Nashville Breast Cohort, with either in situ or invasive disease developing in 27.5% of participants (unpublished data).

MODIFIERS OF RISK

Clinical and Epidemiologic Factors

The younger a woman is when she receives a diagnosis of atypical hyperplasia, the more likely it is that breast cancer will develop (Table 1).[3,5,7] The effect that a family history of breast cancer has on the breast-cancer risk among women with atypical hyperplasia has been controversial. The initial report by Dupont and Page[2] described a subgroup of 39 women with atypical hyperplasia and a family history of breast cancer; these women had a relative risk of breast cancer of 8.9 (95% CI, 4.8 to 17), as compared with a relative risk of 3.5 (95% CI, 2.3 to 5.5) among 193 women with atypical hyperplasia but no family history (Table 1). However, subsequent data from the Nurses' Health Study showed no significant difference in risk according to family history among women with atypical hyperplasia ($P=0.57$).[8] Most recently, Mayo Clinic investigators found no significant difference in risk between 372 women with atypical hyperplasia and no family history of breast cancer and 257 women with atypical hyperplasia and a family history of breast cancer ($P=0.23$).[5,10] Given that many women with atypical hyperplasia have a family history of breast cancer, it is likely that atypical hyperplasia is a tissue phenotype that already reflects the risk inherent in a family history.

Histologic Factors

Two histologic features stratify risk among women with atypical hyperplasia — namely, quantitation of the separate foci of atypical hyperplasia (with greater numbers of foci associated with a higher risk) (Fig. 1C and 2B) and the extent of normal regression (involution) of background lobular units.[5,26,27] The greater the degree of involution, the lower the risk; this pattern has been seen with other types of benign breast disease.[26,27]

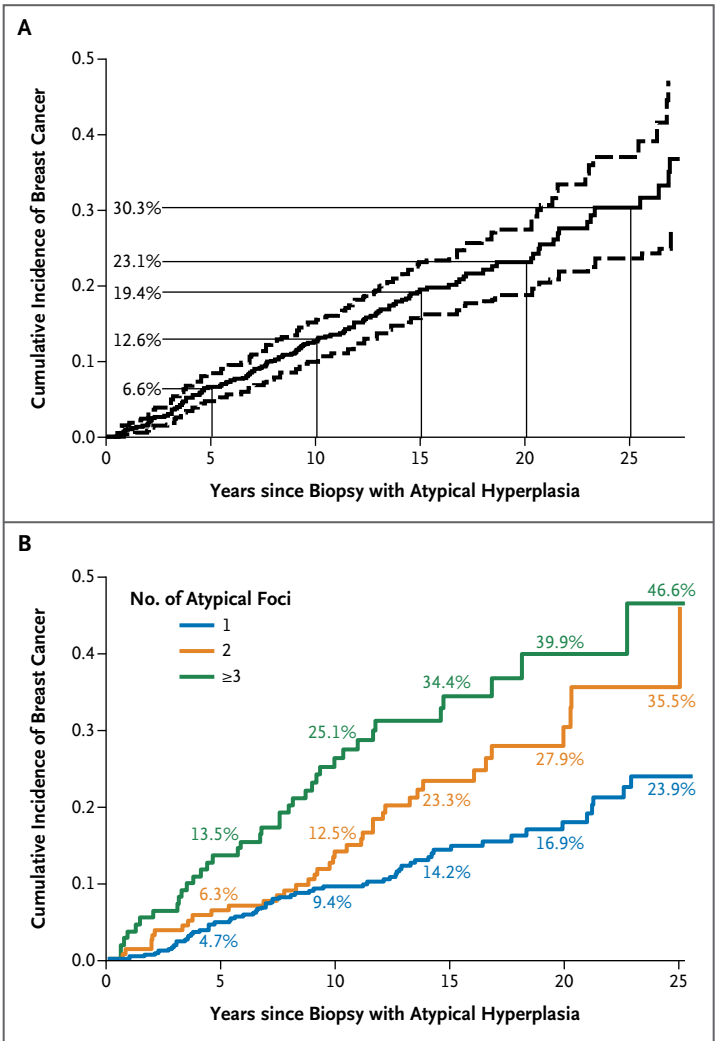

Figure 2. Cumulative Incidence of Breast Cancer after a Diagnosis of Atypical Hyperplasia.

Shown is the cumulative incidence of breast cancer (invasive and ductal carcinoma in situ) after a diagnosis of atypical hyperplasia in the Mayo Clinic cohort (Panel A) and in the same cohort stratified according to the number of foci of atypical hyperplasia (Panel B). The dashed lines in Panel A denote 95% confidence intervals.

FEATURES OF BREAST CANCERS

The most recent data on the types and stages of breast cancer that develop in women with atypical hyperplasia were obtained from the Mayo Clinic cohort.[5] Among 698 women with atypical hyperplasia (Table 1), breast cancer developed in 143 (with 81% of the cancers invasive and 19% ductal carcinoma in situ). Among women with atypical ductal hyperplasia in whom cancer developed, 78% of the later breast cancers were ductal, and 22% were lobular or other histologic types. Among women with atypical lobular hyperplasia in whom cancer developed, 77% of the cancers were ductal and 23% were lobular or other histologic types. Among the 95 women with invasive breast cancer and known nodal status, 75% had node-negative cancer, and 25% had node-positive cancer. A total of 88% of the breast cancers were estrogen receptor–positive. The cumulative incidence of breast cancer appeared to increase linearly over time (Fig. 2).

CLINICAL MANAGEMENT

EXCISIONAL BIOPSY AFTER A CORE-NEEDLE BIOPSY REVEALING ATYPICAL HYPERPLASIA

With the current use of percutaneous core-needle biopsy for diagnosis, when atypical hyperplasia is found, there is a possibility that a cancer was missed as a result of a sampling error. Therefore, surgical excision of the site of the atypical hyperplasia biopsy is recommended in the National Comprehensive Cancer Network (NCCN) guidelines.[28] In the case of atypical ductal hyperplasia, the frequency of finding breast cancer ("upgrading") with surgical excision is 15 to 30% or even higher, despite the use of large-gauge (9- or 11-gauge) core-needle biopsy with vacuum-assisted devices.[29,30] Thus, excision remains the current standard when atypical ductal hyperplasia is identified by core biopsy. However, studies are ongoing to identify situations in which surgical excision of atypical ductal hyperplasia may be avoided.[31] In the case of atypical lobular hyperplasia, reported rates of upgrading have varied from 0 to 67%.[32,33] However, three recent studies suggest that surgical excision is not mandatory for atypical lobular hyperplasia when it is an incidental finding and there is concordance between radiologic and pathological findings regarding the targeted biopsied lesion (in which case upgrading rates are only 0 to 6%).[33,34] Careful clinical and radiologic follow-up is recommended if excisional biopsy is not performed.

RISK PREDICTION

For women with atypical hyperplasia, current practice is to estimate their risk of breast cancer with the use of the Breast Cancer Risk Assessment Tool (BCRAT)[35,36] or the International Breast Cancer Intervention Study (IBIS) model[37] (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

Both models include an adjustment for the relative risk associated with atypical hyperplasia. However, these models have not been validated in women with atypical hyperplasia. In fact, in one study, the BCRAT scores were computed for 331 women with atypical hyperplasia who had long-term follow-up in order to identify later breast cancers,[38] and the concordance between the observed and predicted numbers of cases of invasive breast cancer (C-statistic) was 0.50, which is essentially the same as that expected by chance. The C-statistic for the IBIS model in the same group was also poor, at 0.54 (95% CI, 0.42 to 0.65).[39] The BCRAT significantly underpredicted the risk in women with atypical hyperplasia, whereas the IBIS model significantly overpredicted the risk. Given the poor performance of these models among women with atypical hyperplasia, we think it is preferable to use cumulative incidence data when counseling these women about later breast-cancer risk (Fig. 2A). If the number of foci of atypical hyperplasia is known, the risk can be stratified further (Fig. 2B).

SCREENING

Current guidelines for breast-cancer screening of high-risk women, including guidelines from the NCCN, the American Cancer Society (ACS), and the American College of Radiology, focus primarily on women with hereditary risk.[16,28,40,41] The ACS recommends annual breast MRI as an adjunct to mammography for high-risk patients who have a lifetime breast-cancer risk of approximately 20 to 25% or greater, on the basis of prospective trials of MRI involving women with hereditary risk.[16,40] The ACS guidelines acknowledge that most risk-assessment tools are based on family history. For patients with atypical hyperplasia, the guidelines state that there is insufficient evidence to make recommendations for or against MRI screening; however, they cite a lifetime risk of only 10 to 20% among women with atypical lobular hyperplasia. The ACS does not provide cumulative risk estimates for women with atypical ductal hyperplasia, but they cite a relative risk of 4 to 5 among women in this group.[16]

To our knowledge, the only report of screening MRI in women with atypical hyperplasia, cited by the ACS, is a retrospective study that included 47 women with atypical hyperplasia who underwent MRI (at their physicians' recommendations) and another 79 women who did not.[42] Among the women who were screened, an interval cancer developed after a negative MRI finding in 1 woman, whereas cancer developed in 2 women who were not screened with MRI. More biopsies were performed in the MRI group, and the authors concluded that there was no added value in MRI screening but acknowledged that the number of women with atypical hyperplasia in their study was small. The American College of Radiology cites a lifetime risk of only 15 to 20% among women with atypical hyperplasia and thus concludes that the usefulness of screening these women with MRI is "still in question."[41] NCCN screening guidelines for women 35 years of age or older with a 5-year risk of invasive cancer of 1.7% or greater recommend annual mammograms, clinical breast examinations every 6 to 12 months, and breast awareness.[28] For women with a lifetime risk greater than 20%, as defined by models that are dependent largely on family history, the NCCN guidelines recommend annual breast MRI screening. For women with atypical hyperplasia specifically, they state that there is insufficient evidence to make recommendations for or against MRI screening.

At present, there are no prospective data that address the value of screening MRI for women with atypical hyperplasia; these women should be included in future trials of new imaging strategies for high-risk populations. Given the recently published data on the cumulative risk among women with atypical hyperplasia, which is a level of risk that meets the current standard for MRI screening, as well as the substantial number of women with this diagnosis, it is important that guidelines be updated to include a recommendation for MRI screening in addition to mammography for women with atypical hyperplasia.

PHARMACOLOGIC RISK-REDUCTION

Several randomized clinical trials have evaluated the use of selective estrogen-receptor modulators (SERMs) and aromatase inhibitors (AIs) for the prevention of breast cancer. The NSABP P-1, IBIS-I and II, Royal Marsden, Italian Tamoxifen Prevention Study, MAP.3, and STAR trials (Table 2; for a list of trial abbreviations, see Table S2 in the Supplementary Appendix) were designed specifically as prevention trials with breast cancer as the primary end point.[43-54,61] The MORE, CORE, Generations, RUTH, and PEARL trials

Table 2. Chemoprevention Trials.*

Trial	Agents	All Patients	Patients with Atypical Hyperplasia	Hazard Ratio (95% CI)			Risk Reduction (95% CI) in Group with Atypical Hyperplasia Receiving Active Drug
				For All Breast Cancers	For Invasive Breast Cancer Only	For Noninvasive Breast Cancer Only	
		number					
NSABP P-1, 2005[43]	Tamoxifen and placebo	13,388	1196	NR	0.57 (0.46–0.70)	0.63 (0.45–0.89)	0.25 (0.10–0.52)†
NSABP P-1, 1998[44]	Tamoxifen and placebo	13,175	1193	NR	0.51 (0.39–0.66)	0.50 (0.33–0.77)	0.14 (0.03–0.47)†
Royal Marsden, 1998[45]	Tamoxifen and placebo	2,471	NR	1.06 (0.7–1.7)	NR	NR	NR
Royal Marsden, 2007[46]	Tamoxifen and placebo	2,471	9	0.84 (0.64–1.10)	0.78 (0.58–1.04)	NR	NR
Italian Tamoxifen Prevention Study, 1998[47,48]	Tamoxifen and placebo	5,408	NR	0.84 (0.60–1.17)	0.80 (0.56–1.15)	1.50 (0.53–4.20)	NR
IBIS-I, 2002[49]	Tamoxifen and placebo	7,139	201	0.68 (0.50–0.92)	0.75 (0.54–1.04)	0.31 (0.12–0.82)	NR
IBIS-I, 2007[50]	Tamoxifen and placebo	7,154	NR	0.73 (0.58–0.91)	0.74 (0.58–0.94)	0.63 (0.32–1.20)	NR
IBIS-I, 2011[51]	Tamoxifen and placebo	1,065	NR	NR	NR	NR	0.38 (0.07–2.21)‡
STAR, 2006[52]	Raloxifene and tamoxifen	19,747	4426	NR	1.02 (0.82–1.28)§	1.40 (0.98–2.00)§	No placebo group
STAR, 2010[53]	Raloxifene and tamoxifen	19,471	4432	NR	1.24 (1.05–1.47)§	1.22 (0.95–1.59)§	No placebo group
MAP.3, 2011[54]	Exemestane and placebo	4,560	373¶	0.47 (0.27–0.79)	0.35 (0.18–0.70)	NR	0.36 (0.11–1.12)¶
MORE, 2001[55]	Raloxifene and placebo	7,705	NR	0.38 (0.24–0.58)	0.28 (0.17–0.46)	0.90 (0.30–2.69)	NR
CORE, 2004[56]‖	Raloxifene and placebo	5,213	NR	0.50 (0.30–0.82)	0.41 (0.24–0.71)	1.78 (0.37–8.61)	NR
CORE, 2004[56]**	Raloxifene and placebo	7,705	NR	0.42 (0.29–0.60)	0.34 (0.22–0.50)	1.12 (0.46–2.73)	NR
RUTH, 2006[57]	Raloxifene and placebo	10,101	NR	0.67 (0.47–0.96)	0.56 (0.38–0.83)	2.17 (0.75–6.24)	NR
PEARL, 2010[58]	Lasofoxifene (0.50 mg dose) and placebo	5,704	NR	0.21 (0.08–0.55)	0.17 (0.05–0.57)	0.50 (0.09–2.73)	NR
Generations, 2011[59]	Arzoxifene and placebo	9,354	NR	NR	0.44 (0.26–0.76)	NR	NR
Generations, 2012[60]	Arzoxifene and placebo	9,354	21	0.41 (0.25–0.68)	0.44 (0.26–0.76)	0.30 (0.08–1.09)	NR
IBIS-II, 2014[61]	Anastrozole and placebo	3,864	239‡	0.47 (0.32–0.68)	0.50 (0.32–0.76)	0.30 (0.12–0.74)	0.37 (0.12–1.11)‡††

* NR denotes not reported.
† The risk-reduction estimate is for invasive breast cancer only.
‡ Data are from Jack Cuzick (personal communication).
§ The hazard ratio is for raloxifene relative to tamoxifen.
¶ This group includes patients with either atypical hyperplasia or lobular carcinoma in situ.
‖ These data reflect the 4 years of the CORE trial only.
** These data reflect 8 years of follow-up of the participants in both the MORE and CORE trials.
†† The risk-reduction estimate is for invasive and in situ breast cancers.

examined the effects of the SERMs — raloxifene, lasofoxifene, and arzoxifene — on bone density and fracture risk but included breast cancer as a secondary end point.[55-60] All the studies showed a decreased incidence of breast cancer over a 5-to-7-year period. A meta-analysis recently showed a 38% relative reduction in the risk of breast cancer (invasive and noninvasive) among all the study participants who were enrolled in the SERM randomized trials (hazard ratio, 0.62; 95% CI, 0.56 to 0.69) and a 31% reduction in the incidence of ductal carcinoma in situ (P=0.006).[48] Analyses of data from the subgroup of women with atypical hyperplasia were performed in four of the placebo-controlled trials (NSABP P-1, MAP.3, IBIS-I, and IBIS-II). A total of 2009 women with atypical hyperplasia were randomly assigned to receive an active agent or placebo in those trials (Table 2). Relative-risk reductions in the atypical hyperplasia subgroup ranged from 41 to 79%, which suggested an even greater benefit than in the total population treated with active agent in those trials (Table 2).

An important consideration is the side-effect profile of these agents. To quantify the incidence of "attributable" or "excess" side effects, we subtracted the incidence of side effects in the placebo groups from the incidence in the active-treatment groups and expressed the results as the number per 1000 women during the study follow-up period (usually 5 years) (Table 3). The major risks that occur in association with all SERMs are venous thromboembolisms, with the risk of deep-vein thromboses slightly exceeding that of pulmonary emboli. The excess incidence of venous thromboembolisms during the 5 to 7 years of follow-up ranges from 5.9 to 14 per 1000, when only statistically significant differences are considered. The higher attributable risks generally occurred in older women. Tamoxifen, but not the other SERMs, is associated with an increased risk of endometrial cancer, with a significant excess incidence of 5.5 per 1000 women (and a lower risk in premenopausal women than in postmenopausal women).[62] Vasomotor symptoms are seen in many women who receive treatment with SERMs or AIs, with attributable risks of 67 per 1000 (MAP.3 trial) to 117 per 1000 (NSABP P-1 trial).[43,44,54] A benefit of treatment with all the SERMs is a significant reduction in the risk of fractures. With the AIs, there is a trend toward an increased risk of fractures that does not reach significance. Published reviews help define the balance between the benefits and risks associated with breast-cancer chemoprevention according to age group and clearly show enhanced benefits for women who are at higher risk.[63,64]

Even though the benefit:risk ratios for chemopreventive agents are favorable for many women, studies show that these agents are infrequently prescribed and infrequently used.[17] Waters et al.,[17] using data from the National Health Interview Survey (2010), found a 0.03% prevalence of tamoxifen use for chemoprevention among U.S. women 35 to 79 years of age and a 0.21% prevalence of raloxifene use among women 50 to 79 years of age. Studies focusing on high-risk women show that many physicians are reluctant to prescribe the agents,[65] in some cases because they feel insufficiently informed about the drugs.[66] Numerous other studies have documented the reluctance of women — even women who are considered at high risk[65,67] — to take tamoxifen, mainly because of a fear of side effects.

Research in patient decision making has shown that patients' perceived level of risk is a major determinant of their willingness to accept chemoprevention.[68] Among women with atypical hyperplasia specifically, it is likely that the low rate of the use of chemopreventive agents stems, at least in part, from an insufficient understanding of their cumulative risk of breast cancer.

Adjuvant tamoxifen is now considered as a treatment option for women with estrogen-receptor–positive ductal carcinoma in situ.[69,70] The high level of estrogen-receptor expression in atypical hyperplasia[25] and the estrogen-receptor positivity of the large majority of breast cancers that develop in women with atypical hyperplasia provide additional rationale for the use of antiestrogen therapy for prevention.

With respect to pharmacologic risk reduction, the American Society of Clinical Oncology guideline states that for women with a 5-year projected absolute risk of breast cancer of 1.7% or higher, the use of a chemopreventive agent should be discussed (tamoxifen for premenopausal or postmenopausal women and raloxifene or exemestane for postmenopausal women).[62] Women with atypical hyperplasia clearly meet this risk criterion with their cumulative risk of approximately 1% per year. The NCCN guideline for risk reduction also uses the threshold of a

Table 3. Excess or Reduced Side Effects with Various Chemopreventive Agents versus Placebo.*

Trial	Active Agent	No. of Participants		Change in Incidence†								
		Active	Placebo	Death	VTE	DVT	PE	CV	CVA	TIA	EC	Fractures
SERM trials												
NSABP P-1, 2005[43]	Tamoxifen	6597	6610	1.8	NR	2.2	2.3‡	0.6	3.1	−0.5	5.5‡	−5.5‡
IBIS I, 2007[50]	Tamoxifen	3579	3575	2.8	14‡	8.7‡	NR§	NR	0.8	−1.4	1.7	1.4
Italian Tamoxifen Prevention Study[47]	Tamoxifen	2700	2708	−0.7	5.9‡	NR	NR	NR	1.4	0.4	NR	NR
Royal Marsden[45,46]	Tamoxifen	1238	1233	0	4.0	NR	NR	−1.6	−1.6	NR	6.7	−2.4
CORE[56]	Raloxifene	5129	2576	−2.1	4.1	2.1	2.5‡	NR	NR	NR	−0.2	NR
MORE[55]	Raloxifene	5111	2571	NR	NR	NR	NR	NR	NR	NR	NR	−2.5‡
RUTH[57]	Raloxifene	5044	5057	−0.2	6.3‡	3.6	2.4	NR	5.0	NR	0.8	−6.5‡
Generations[59,60]	Arzoxifene	4678	4676	1.5	7.7‡	3.6‡	1.9	0.6	1.0	NR	1.1	−15‡
PEARL 0.25[58]	Lasofoxifene	2729	2740	9.1	11‡	NR	3.7‡	−8.0	−6.8‡	1.8	−0.4	−38‡
PEARL 0.5[58]	Lasofoxifene	2745	2740	2.9	6.9‡	NR	2.5	−11‡	−6.5‡	0	−0.4	−52‡
AI trials												
MAP.3[54]	Exemestane	2285	2275	0	1.7	NR	NR	2.1	0.9	NR	−1.3	2.6
IBIS-II[61]	Anastrozole	1920	1944	1.0	1.0	NR	NR	−0.5	−1.6	NR	−1.0	7.9

* The table is adapted from Tables 3, 4, 5, and 6 in the article by Visvanathan et al.[62] Data for IBIS-II are adapted from Cuzick et al.[61] Not included in the original tables were data on hot flushes and joint pain. Regarding these symptoms, the incidence of excess joint pain was 22 per 1000 women (P=0.04) in the exemestane prevention trial (MAP.3).[54] The incidence of excess hot flushes was 67 per 1000 (P<0.001) and 117 per 1000 (P value not stated) in the MAP.3 and NSABP P-1 trials, respectively.[43,44,54] AI denotes aromatase inhibitor, CV cardiovascular complications, CVA cerebrovascular accident, DVT deep-vein thrombosis, EC endometrial cancer, PE pulmonary embolism, SERM selective estrogen-receptor modulator, TIA transient ischemic attack, and VTE venous thromboembolism.

† Data are the excess of (positive numbers) or reduction in (negative numbers) events in each trial during the study follow-up period (usually 5 years), expressed as the number per 1000 study participants, comparing participants receiving the active agent with those receiving placebo.

‡ The result is significant.

§ In this study, PE was grouped together with DVT.

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5-year risk of 1.7% or higher but adds a life expectancy of 10 years or longer for the consideration of risk-reduction interventions, including the use of pharmacologic agents.[71] The recommendations of the U.S. Preventive Services Task Force on the use of tamoxifen or raloxifene for the reduction of breast-cancer risk[72] conclude that there is moderate certainty of a moderate net benefit from the use of these agents in women at increased risk for the disease. They reference studies showing that women with a higher risk status (e.g., an estimated 5-year risk of 3% or greater) are most likely to benefit.[63]

SURGICAL RISK-REDUCTION

NCCN guidelines state that bilateral prophylactic mastectomy should generally be considered only for women who have a genetic predisposition to breast cancer or possibly those who have been treated with thoracic radiation before 30 years of age or who have a history of lobular carcinoma in situ.[71] The Society of Surgical Oncology recognizes atypical hyperplasia as a possible but not routine indication for bilateral prophylactic mastectomy.[73] In one small, retrospective study, atypical hyperplasia was the indication for the procedure in 11 of 46 patients (24%) who had not undergone BRCA testing and were undergoing risk-reduction surgery.[74] In current practice, with minimal data available on this topic and with chemopreventive agents for risk reduction available, atypical hyperplasia is generally not an indication for prophylactic mastectomy.

CONCLUSIONS AND RECOMMENDATIONS

Currently, for best practice, clinicians should understand that atypical hyperplasia confers an absolute risk of later breast cancer of 30% at 25 years of follow-up. Frequently used risk-prediction models, such as the BCRAT and IBIS models, do not provide accurate risk estimates for women with atypical hyperplasia. Absolute risk data should be used in place of models to describe breast-cancer risk in this population. Guidelines for high-risk women should be updated to include women with atypical hyperplasia; screening MRI should be considered an option for them, to be performed in addition to mammography. Randomized, controlled trials have shown pharmacologic risk reduction to be effective in women with atypical hyperplasia, yet only a small minority of women use chemopreventive agents. Education regarding chemoprevention should describe a woman's absolute risk of breast cancer, the anticipated reduction in risk, and the absolute risks of various side effects.

Additional research is needed to advance the understanding and management of atypical hyperplasia. First, accurate diagnosis is essential, and quality-control studies are needed to ensure the application of standardized pathological criteria. Women with atypical hyperplasia should be included in future trials of new imaging strategies. Behavioral studies can improve methods of communicating complex information on risk and management options to these women. Additional research will also help to advance our understanding of the molecular aspects of atypical hyperplasia in order to identify new biomarkers that can predict different subtypes of breast cancer and varying time frames of risk, as well as possible new pathways for prevention. Another important issue for women with atypical hyperplasia concerns their risk of death from breast cancer versus their risk of death from other causes. In fact, breast cancer will not develop in the majority of these women. Even among those in whom breast cancer does develop, the diagnosis may occur at an age at which their risk of death from other causes is higher than their risk of death from breast cancer.

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