

Atypical hyperplasia of the breast: Cancer risk-reduction strategies

📌 Women with atypical hyperplasia are at increased risk for breast cancer. We need to characterize that risk for patients and ensure appropriate screening and cancer risk-reduction strategies. Here, recommendations for clinical practice.

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Of the approximately 1 million benign breast biopsies obtained annually from US women, some 10% yield a diagnosis of atypical hyperplasia, microscopically classified as ductal or lobular. Atypical hyperplasia represents a “proliferation of dysplastic, monotonous epithelial-cell populations that include clonal subpopulations. In models of breast carcinogenesis, atypical hyperplasia occupies a transitional zone between benign and malignant disease,” write Hartmann and colleagues, the authors of a recent special report in the *New England Journal of Medicine*.¹

Long-term follow-up studies have found atypical hyperplasia to confer a relative risk for breast cancer of 4.0. Although these findings are well established, the cumulative *absolute*

risk for breast cancer conferred by a diagnosis of atypical hyperplasia only recently has been described. Hartmann and colleagues note that it approaches 30% over 25 years.¹

Recommendations for clinical practice

The authors of this special report do a service to women and their clinicians by pointing out the high long-term risk of malignancy faced by women with atypical hyperplasia of the breast. They also make a number of important recommendations for practice:

- **When counseling patients with this diagnosis, it is preferable to use cumulative incidence data** because the most commonly used breast cancer risk-prediction models do not accurately estimate the risk for breast malignancy in women with atypical hyperplasia.
- **When atypical hyperplasia of the breast is found after core-needle biopsy (FIGURE, page 20), surgical excision of the site is recommended** to ensure that cancer was not missed as a result of a sampling error. This recommendation derives from National Comprehensive Cancer Network (NCCN) guidelines.² “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

IN THIS ARTICLE

Dr. Samiian: How I counsel patients about their management options

[page 18](#)

Mammography shows microcalcifications

[page 20](#)



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CONTINUED ON [PAGE 18](#)

Here's how I counsel patients with atypical hyperplasia about their management options

Risk assessment of a patient with atypia of the breast requires consideration of multiple factors. Although cumulative risk is now better defined, I still find the risk-assessment models to be valuable decision-making tools.

When chemoprevention may be in order

If the 5-year risk of breast cancer by the Gail model is greater than 1.7%, and the patient is older than 35 years, I counsel her that she qualifies for chemoprevention with prophylactic endocrine therapy with the selective estrogen receptor modulators tamoxifen or raloxifene, or the aromatase inhibitor exemestane.¹ The choice of drug depends on her menopausal status, bone mineral density, and presence of other comorbidities.

Although tamoxifen is indicated for breast cancer chemoprophylaxis in premenopausal and postmenopausal women, raloxifene is only approved for risk reduction in postmenopausal women. Likewise, aromatase inhibitors (which have shown high efficacy in chemoprophylaxis but are not FDA-approved for this indication) should be used only in postmenopausal women.

Who might gain the most from tamoxifen? The tamoxifen risk/benefit calculator^{2,3} can be used to weigh the benefit of breast cancer prevention against the risk of the drug's adverse effects. Life-threatening adverse effects can include thromboembolic events and endometrial malignancy.^{2,3} Based on recommendations from the US Preventive Services Task Force, **women with a 5-year risk of breast cancer equal to or greater than 3% are most likely to benefit from 5 years of prophylactic endocrine therapy.**² In women who are posthysterectomy, the benefit/risk ratio associated with tamoxifen use is higher.

When is annual MRI appropriate?

The decision to perform annual screening breast MRI should be based on a strong family history rather than strictly a biopsy diagnosis of atypia. The Claus and BRCAPRO models are more appropriate here, as they use only family history information and do not incorporate biopsy results. There are no data to support the use of screening breast MRI in patients with atypia who do not have a strong family history or a deleterious genetic mutation.^{4,5}

Patients with proliferative breast disease tend to have a substantial amount of vague glandular enhancement on breast MRI. Screening MRI in patients with atypia is more likely to lead to frequent false-positive results and unnecessary benign biopsies and cause significant patient anxiety. Without endocrine blockade, breast MRI in this population tends to be nondiagnostic, with a very low yield for breast cancer diagnosis (positive predictive value, 20%).⁶ Repeated false-positive results of screening MRI in this population can cause patient anxiety, culminating

in unnecessary mastectomies. **If the Claus or BRCAPRO models yield a lifetime risk for breast cancer above 20%, or the breasts are extremely dense, I discuss with my patient the possibility of adding screening breast MRI.**

When ordering breast MRI, it's important to be aware that this imaging requires gadolinium intravenous contrast, which is excreted through the kidney and requires adequate renal function. This contrast agent can lead to nephrosclerosis in patients with renal insufficiency. In patients with hypertension, diabetes, age over 60, or prior chemotherapy, a recent serum blood urea nitrogen/creatinine level is required. Therefore, the decision to perform annual breast MRI for the rest of a woman's life should not be taken lightly.

As a part of comprehensive risk assessment, it is important to identify patients who qualify for genetic testing. The addition of screening breast MRI should be heavily dependent on family history, results of BRCA testing and, possibly, mammographic breast density.

Make sure your patient knows that her condition places her at elevated risk, and refer her to a breast specialist

It's also important to involve the patient in decision making to help ensure that she is proactive and adherent when choosing the best way to manage her risk. The key is to educate her about the importance of atypia.

Many women are told that their follow-up surgical excision was "benign," and the subject of "atypia" or risk reduction is never addressed. It's important that the right diagnostic terminology and coding are documented in the medical record so that the finding of atypia is not downgraded to a "benign breast biopsy."

Finally, due to the complexities of this issue, evaluation by a qualified breast specialist or high-risk cancer program is recommended.

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Mammography shows microcalcifications



A cluster of pleomorphic microcalcifications demonstrate atypical ductal hyperplasia after stereotactic core needle biopsy.

the use of large-gauge (9- or 11-gauge) core-needle biopsy with vacuum-assisted devices,” Hartmann and colleagues note.

- **Women with atypical hyperplasia clearly should receive annual mammographic screening.** Although screening magnetic resonance imaging (MRI) may play a role in assessing women with this diagnosis, no prospective trial data have evaluated its utility in this setting. Screening MRI’s low specificity may lead to many unnecessary biopsies with benign findings. This in turn can generate so much anxiety that women may pursue prophylactic bilateral mastectomy to avoid a lifetime of stress related to breast cancer concerns. Women with atypical hyperplasia should be included in future trials of new breast imaging technologies.
- As with other high-risk women, **those who have been diagnosed with atypical hyperplasia are well served by being referred to and followed by a physician with special expertise in breast disease** who can arrange appropriate screening and follow-up. (See the sidebar, “Here’s how I counsel women with atypical hyperplasia about their management options.”)
- **Women with a history of atypical hyperplasia who are considering initiation of systemic menopausal hormone therapy**

should be aware that they have a higher baseline risk for invasive breast cancer than other women. Accordingly, the absolute risk of invasive breast cancer associated with use of estrogen-progestin menopausal hormone therapy (EPT) is also likely substantially higher than in average-risk women. Therefore, among women with a history of atypical hyperplasia of the breast who have an intact uterus, use of EPT should be minimized.

- **Selective estrogen receptor modulators such as tamoxifen and raloxifene should be more widely used** by women with atypical hyperplasia because of their ability to reduce breast cancer risk. Aromatase inhibitors also should be prescribed more widely in this population. (Again, see the sidebar, “Here’s how I counsel women with atypical hyperplasia about their management options.”)

Most women will not develop breast malignancy

As Hartmann and colleagues point out, all is not dire once a woman is diagnosed with atypical hyperplasia of the breast. In most of these women, breast cancer will not develop—and if it does develop, it may occur at an age when mortality from other causes is more likely than from breast cancer. In this respect, women with atypical hyperplasia of the breast are different from carriers of BRCA mutations. Although women with atypical hyperplasia as well as mutation carriers are both at high lifetime risk for breast cancer, breast malignancies occur at an earlier age in mutation carriers. Accordingly, as the authors of this special report advise, in general, a diagnosis of atypical hyperplasia should not be considered an indication for risk-reducing bilateral mastectomy. 📌

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FAST TRACK

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