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# Atypical hyperplasia of the breast: Clinical cases and management strategies

## ABSTRACT

Atypical hyperplasia of the breast is a histopathologic lesion identified incidentally on image-guided breast biopsy. It is associated with a substantial increase in lifetime risk for breast cancer. Clinicians should counsel women with atypical hyperplasia regarding risk-reducing strategies, which include preventive endocrine therapy options, enhanced surveillance imaging, and lifestyle modifications. In this review, we describe 5 different but common clinical case scenarios for atypical hyperplasia of the breast and review management strategies for each scenario.

## KEY POINTS

For patients with atypical ductal hyperplasia identified on core needle biopsy, surgical consultation is recommended to discuss if surgical excision is warranted based on radiology and pathology concordance, owing to significant risk of finding an associated in situ or invasive malignant lesion.

Observation instead of surgical excision may be considered for atypical lobular hyperplasia without other high-grade lesions if the radiologic and pathologic findings are concordant.

Flat epithelial atypia without an associated high-risk lesion does not require discussion of risk-reducing endocrine therapy unless formal risk assessment using a model largely dependent on family history suggests otherwise.

**A**TYPICAL HYPERPLASIA of the breast is a high-risk benign breast lesion that carries an increased lifetime risk for invasive breast cancer.<sup>1</sup> Breast biopsies are commonly performed in the United States. Follow-up of mammographic abnormalities with image-directed breast biopsy has shown atypical hyperplasia as an incidental finding in 10% of cases.<sup>2</sup> Histopathologically, atypical hyperplasia is classified as atypical ductal hyperplasia (ADH) or atypical lobular hyperplasia (ALH). Other findings distinct from classical atypical hyperplasia are lobular carcinoma in situ, classified as lobular neoplasia or flat epithelial atypia (FEA).<sup>2</sup>

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For women with atypical hyperplasia, the cumulative breast cancer risk is approximately 1% per year.<sup>2,3</sup> Breast cancer risk calculators available to quantify breast cancer risk include the Breast Cancer Risk Assessment Tool (BCRAT),<sup>4</sup> which is also known as the Gail model,<sup>5</sup> and the International Breast Cancer Intervention Study (IBIS),<sup>6</sup> which is also known as the Tyrer-Cuzick Model Breast Cancer Risk Evaluation Tool. These models provide population-level estimated 5-year (BCRAT), 10-year (IBIS), and lifetime breast cancer risk. However, the BCRAT calculator can underestimate risk for atypical hyperplasia,<sup>3,7</sup> whereas the IBIS model has been shown to significantly overestimate risk, particularly for patients with a family history of breast

**TABLE 1**  
**Management of high-risk breast lesions**

| High-risk breast lesion      | Rate of upgrade to invasive breast cancer | Management after core needle biopsy                                                               | Use of risk-reducing endocrine therapy                                                                                            |
|------------------------------|-------------------------------------------|---------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|
| Atypical ductal hyperplasia  | 10% to > 30% <sup>14,15</sup>             | Observation if radiologic and pathologic findings are concordant or after excisional biopsy       | Yes                                                                                                                               |
| Atypical lobular hyperplasia | 0% to 67% <sup>17</sup>                   | Observation if radiologic and pathologic findings are concordant or consider an excisional biopsy | Yes                                                                                                                               |
| Flat epithelial atypia       | 0% to 21% <sup>16</sup>                   | Observation if radiologic and pathologic findings are concordant or consider an excisional biopsy | Assess breast cancer risk factors and use available risk-assessment calculators (BCRAT or IBIS)<br>Yes, if there is elevated risk |

BCRAT = Breast Cancer Risk Assessment Tool; IBIS = International Breast Cancer Intervention Study

cancer and ADH, as the risk of family history is compounded by the risk due to atypia.<sup>2,3</sup> Currently, the US Preventive Services Task Force recommends discussing risk-reducing recommendations with patients who have estimated BCRAT 5-year risk greater than 3%,<sup>8</sup> and the National Comprehensive Cancer Network recommends discussing therapies such as annual mammograms and clinical breast examinations every 6 to 12 months for women age 35 or older and with 5-year risk 1.7% or greater.<sup>7,8</sup> The American Cancer Society recommends magnetic resonance imaging (MRI) breast screening for patients with a calculated lifetime breast cancer risk of at least 20% based on IBIS.<sup>9</sup> The American College of Radiology and National Comprehensive Cancer Network currently recommend that MRI screening be considered in addition to annual mammography for women with atypical hyperplasia.<sup>10,11</sup> Because studies show that the lifetime risk of breast cancer is greater than 20% for women with atypical hyperplasia, the role of annual MRI plus mammography surveillance is appropriate.<sup>7,12</sup>

Primary care practitioners may receive pathology reports that describe these lesions after breast biopsies. Therefore, we review 5 different case scenarios that primary care practitioners may encounter and include information on lesion presentation, management options, and clinical pearls for each case.

## ■ CASE 1

A 50-year-old woman presented to the office after abnormal mammographic screening of her right breast, which revealed a 6-mm cluster of calcifications

in the upper outer quadrant. An image-guided core needle biopsy showed ADH involving 3 foci. She had a family history of breast cancer: her mother was diagnosed at age 58 and 1 of 2 maternal aunts was diagnosed at age 62.

## Discussion

ADH is a marker for increased risk of breast cancer. When identified on core needle biopsy, ADH carries a risk of unsampled malignancy.<sup>13,14</sup> At the time of excisional biopsy, rates of upgrade to in situ or invasive malignancy range from 10% to more than 30% (Table 1)<sup>14–17</sup> for high-risk breast lesions.<sup>13,15–19</sup> Because of these upgrade rates, the current recommendation is for an excisional biopsy for ADH identified on core needle biopsy, although there may be some cases wherein more than 90% of the lesion is removed by biopsy and no other high-risk features exist. In these cases, excision is not required.<sup>20</sup>

If an excisional biopsy does not identify higher-grade lesions (in situ carcinoma, invasive carcinoma), patients should be counseled regarding risk-reducing endocrine therapy for 5 years. In a Mayo Clinic cohort study of 698 women with atypical hyperplasia of the breast, cumulative incidence of breast cancer at 25 years was 29%.<sup>2</sup> This risk can be further stratified based on the number of foci seen on pathology.<sup>2,7</sup> A 1985 study by DuPont and Page<sup>21</sup> followed more than 3,300 women with benign breast biopsies for a median of 17 years and showed that patients with atypical hyperplasia and family history were at significantly increased risk compared with those without a family history of breast cancer. However,

the Nurses' Health Study and the Mayo Clinic cohort study, both large studies, showed no significant risk difference for women with a family history of breast cancer.<sup>2,3,7,22</sup> Subgroup analyses of several large clinical trials (National Surgical Adjuvant Breast and Bowel Project, Prevention Trial [NSABP P-1], Mammary Prevention 3 [MAP.3], and IBIS-I and II) showed significant risk reduction for women with ADH taking selective estrogen receptor modulators (up to 86%)<sup>23</sup> or aromatase inhibitors (41% to 79%)—an even greater benefit than for women with a calculated high risk (38% relative risk reduction).<sup>7,24,25</sup>

### Clinical pearls

- For patients with ADH identified on core needle biopsy, surgical consultation is recommended to discuss if surgical excision is warranted based on radiology and pathology concordance, owing to significant risk of finding an associated in situ or invasive malignant lesion.
- Risk-reducing endocrine therapy should be discussed with patients because of increased lifetime risk of breast cancer, estimated at 1% per year.

### CASE 2

A 60-year-old woman underwent routine screening mammography that revealed heterogeneously dense breasts and a 5-mm cluster of calcifications identified in the upper inner quadrant of the right breast. Image-guided core needle biopsy showed ALH, and the radiologic findings correlate with the histopathologic findings on the core needle biopsy, confirming concordance. Patient history noted osteoporosis in the lumbar spine, with the lowest T-score of −2.8 and history of uterine hyperplasia without atypia.

### Discussion

ALH is usually found in less than 1% of breast core needle biopsies.<sup>14</sup> The absolute risk of developing breast cancer after a diagnosis of ALH is approximately 1% per year or approximately 30% at 25-year follow-up.<sup>3,7,14</sup>

Rates of upgrade to in situ or invasive disease at ALH excision varied substantially among studies. A systematic review of 65 studies revealed that upgrade to any malignancy ranged from 0% to 67% for excised lesions.<sup>17</sup> Because of this wide variation, routine surgical management of ALH has been controversial. More recent studies suggested that surgical excision is not always indicated for ALH if radiologic and pathologic findings are concordant, and no other coexisting high-risk lesions requiring excision are found.<sup>14</sup> As

with ADH, risk-reducing endocrine therapy for the prevention of breast cancer is associated with a 41% to 79% relative risk reduction for women with ALH.<sup>3,7,23</sup> The approach to discussing risk-reducing endocrine therapy for women with atypical hyperplasia should be individualized according to menopausal status, medical comorbidities, and risk of adverse effects.

In this case scenario, the patient has several relevant comorbidities, osteoporosis, and a history of uterine hyperplasia without atypia. Thus, there is a need to balance the benefits of risk-reducing endocrine therapy vs the risk of adverse effects of medications. Tamoxifen can be used for premenopausal and postmenopausal women; however, tamoxifen carries the risk of endometrial cancer, venous thromboembolism, and cataracts. For endometrial cancer, tamoxifen was shown to have a 9 per 1,000 risk of uterine cancer compared with a risk of 4.0 per 1,000 for the general population of US women ages 50 to 59.<sup>26</sup> Therefore, for this patient with an intact uterus and a history of uterine hyperplasia, tamoxifen should be considered cautiously. This patient also has osteoporosis, so an aromatase inhibitor would not be the best choice because of the association of aromatase inhibitors with reduced bone density. The Study of Tamoxifen and Raloxifene P-2 trial compared the effectiveness of tamoxifen and raloxifene vs placebo. Initial results from this trial revealed similar effectiveness of raloxifene and tamoxifen in reducing the risk of invasive breast cancer. An updated analysis with an 81-month median follow-up showed a 38% reduced risk of invasive breast cancer with raloxifene and 50% with tamoxifen compared with placebo.<sup>27</sup>

Raloxifene was not associated with an increased risk of invasive uterine cancer or uterine hyperplasia compared with tamoxifen. The rates of venous thromboembolism were lower with raloxifene than tamoxifen (2.4 vs 3.3 per 1,000, respectively) as was the development of cataracts (20% less). With the 60 months of treatment plus additional 21 months of follow up, raloxifene appeared to retain 76% of the effectiveness of tamoxifen in preventing invasive disease and grew closer over time to the effectiveness of tamoxifen in preventing noninvasive disease with fewer adverse effects.<sup>27</sup>

Raloxifene has been approved to prevent and treat postmenopausal osteoporosis and can provide secondary benefit for breast cancer risk reduction beyond 5 years if it is being prescribed for osteoporosis management. Vasomotor symptoms can be exacerbated with both selective estrogen receptor modulators and aromatase inhibitors. The National Comprehensive Can-

cer Network guidelines for high-risk women include breast awareness, clinical breast examination every 6 to 12 months (minimum 12-month follow-up), annual screening mammography with possible tomosynthesis (not before age 30), and possible annual breast MRI beginning at diagnosis of ALH (not before age 25).<sup>11,15</sup> Contrast-enhanced mammography or whole-breast ultrasonography could be considered for those who qualify but cannot undergo MRI.

## Clinical pearls

- Observation instead of surgical excision may be considered for ALH without other high-grade lesions if the radiologic and pathologic findings are concordant.
- Risk-reducing endocrine therapy should be discussed with patients who have ALH.
- Raloxifene is a good choice for patients with ALH and a history of uterine hyperplasia with atypia or osteopenia or osteoporosis.
- Supplemental screening with annual breast MRI or other imaging options, such as contrast-enhanced mammography or whole-breast ultrasonography for those who qualify but cannot undergo MRI should be considered for patients with ALH.

## CASE 3

A 40-year-old premenopausal woman with a strong family history of breast cancer presented to your office after her first screening mammogram that showed 4-mm grouped amorphous calcifications in the left-to-central breast. Focused left breast ultrasonography showed no sonographic correlation. A left breast stereotactic biopsy was performed, and pathologic findings revealed flat FEA. Postbiopsy mammography confirmed removal of all calcifications. Radiologic and pathologic findings were concordant. The patient was seeking advice on management and surveillance of FEA.

## Discussion

FEA, considered to be a precursor to breast cancer development, is a rare columnar cell breast lesion typically diagnosed on breast biopsies of calcifications identified on screening mammography. These lesions, which occur in 0.7% to 12.2% of percutaneous breast biopsies,<sup>28</sup> have enlarged terminal ductal lobular units lined by up to several layers of columnar epithelial cells with low-grade cytologic atypia and no architectural distortion. Although FEA may be associated with luminal calcifications,<sup>29</sup> no clinical features are present in patients with FEA.

The reported upgrade rate of FEA to ductal carcinoma in situ or invasive carcinoma following core needle biopsy to time of excision is wide-ranging, from 0% to 42%,<sup>16,28</sup> which has resulted in controversy regarding the need for surgical excision or observation of these lesions.<sup>16</sup> The amount of tissue sampled differed (core needle diameter, use of vacuum-assisted technique, and excisional biopsy quality) when comparing studies and was the suggested variable responsible for the broad difference in upgrade rate. Radiologic and pathologic concordance and improved tissue sampling showed an upgrade rate of less than 3% with pure FEA.<sup>30</sup> Residual calcifications after biopsy have been associated with an increased upgrade rate.<sup>16</sup> A recent meta-analysis of 42 studies showed a pooled upgrade rate of 1% for invasive carcinoma and 2% for ductal carcinoma in situ.<sup>31</sup> The upgrade rate was 0% when more than 90% of calcifications were removed with core needle biopsy.<sup>31</sup> The National Comprehensive Cancer Network suggests observation is acceptable in select patients with FEA,<sup>32</sup> for patients with radiologic-pathologic concordance when all microcalcifications are removed at biopsy and no associated mass or high-risk lesions exist.<sup>32</sup> Otherwise, patients should be referred to a breast specialist for consideration of surgical excision of FEA.

FEA frequently occurs in association with high-risk lesions such as ADH, ALH, or lobular carcinoma in situ and is most often identified with concurrent ADH.<sup>14</sup> A recent meta-analysis, however, showed a 17% rate of concurrent ADH and FEA.<sup>31</sup> The risk of upgrade at surgical excision to ALH or lobular carcinoma in situ was lower: 4.8% and 2.9%, respectively.<sup>33</sup> FEA associated with ADH, ALH, or lobular carcinoma in situ is clinically significant, and identifying one of these high-risk lesions should prompt high-risk surveillance and preventive strategies.<sup>31</sup>

The long-term risk of breast cancer for pure FEA is only mildly increased (relative risk, 2.0),<sup>34</sup> a risk similar to that of proliferative breast disease without atypia. If the excisional biopsy does not show findings of ALH or ADH, risk-reducing endocrine therapy or surveillance with high-risk breast imaging is not required for pure FEA. However, if a validated risk assessment model suggests an increased risk of breast cancer based on family history, patients can be counseled about risk-reducing endocrine therapy.

In this case, surgical excision is not indicated based on isolated FEA and a low risk of upgrade due to radiologic and pathologic concordance and removal of all calcifications on biopsy. Because of the strong family history of breast cancer, a formal risk assessment is

needed using a model largely dependent on family history, such as the Tyrer-Cuzick model (IBIS)<sup>6</sup> or CanRisk (<https://www.canrisk.org/>). If the patient's lifetime risk of breast cancer is 20% or greater, annual high-risk screening MRI and mammography are recommended, and risk-reducing medications should be offered.

### Clinical pearls

- Imaging surveillance without surgical excision is reasonable after FEA on core needle biopsy without concurrent high-risk lesions and with radiologic-pathologic concordance.
- FEA without an associated high-risk lesion does not require discussion of risk-reducing endocrine therapy unless formal risk assessment using a model largely dependent on family history suggests otherwise.

### CASE 4

A 42-year-old premenopausal woman underwent a left breast excisional biopsy that revealed ADH. After she was counseled regarding risks and benefits of tamoxifen, she started therapy at 20 mg per day. After 3 years of tamoxifen therapy, she returned with concerns about 3 months of irregular and heavy menstrual bleeding. Her body mass index was 32.1, was nulliparous, and had a history of polycystic ovary syndrome. She reported being sexually active with her male partner. Pelvic ultrasonography showed 2 small endometrial polyps, and the endometrial lining was 12-mm thick. An endometrial biopsy revealed atypical endometrial hyperplasia. Tamoxifen was discontinued, and she subsequently underwent dilation and curettage and hysteroscopy with polypectomy. To preserve fertility, she deferred hysterectomy.

### Discussion

In estrogen-depleted postmenopausal women, tamoxifen has proestrogen effects on the endometrium, but in premenopausal women with adequate estrogen levels, tamoxifen exhibits an estrogen antagonist effect on the endometrium.<sup>35</sup> For women on tamoxifen therapy, endometrial cancer or hyperplasia is less common in premenopausal than postmenopausal women.<sup>36</sup> However, in some premenopausal patients, tamoxifen can cause endometrial subepithelial stromal hypertrophy, leading to irregular menstrual bleeding, which is common, and other uterine pathologic findings such as endometrial polyps and hyperplasia. Endometrial cancer is less common.<sup>37</sup>

Results of a recent review of Cochrane controlled trials showed the risk of endometrial cancer for women

under age 50 taking tamoxifen to be only slightly greater than placebo, with a relative risk 1.19 and 95% confidence interval (CI) 0.53–2.65 ( $P = .60$ ).<sup>38</sup> However, in a recent large retrospective Korean study of over 78,320 premenopausal breast cancer patients, those treated with tamoxifen vs placebo had higher rates of uterine pathologic findings.<sup>39</sup> These patients were followed for a mean 6.13 years and were shown to have increased rates of endometrial polyps (20.13 cases per 1,000 person-years), endometrial hyperplasia (13.49 cases per 1,000 person-years), and endometrial cancer (2.01 cases per 1,000 person-years).<sup>39</sup> The American College of Obstetricians and Gynecologists recommends against routine surveillance testing of asymptomatic patients, but all premenopausal and postmenopausal patients presenting with abnormal uterine bleeding while taking tamoxifen should receive additional diagnostic evaluation.<sup>40</sup> A meta-analysis evaluating tamoxifen use by the Early Breast Cancer Trialists' Collaborative Group showed an increased incidence of endometrial cancer in women over age 55.<sup>41</sup> The Adjuvant Tamoxifen, Longer Against Shorter trial was designed to study tamoxifen use at 5 vs 10 years and found significantly higher risk of endometrial cancer in postmenopausal women (relative risk, 1.74 [95% CI, 1.30–2.34]), suggesting a cumulative dose effect.<sup>42</sup> In addition to age and duration of therapy, irregular and abnormal uterine bleeding are considered risk factors for endometrial hyperplasia.

Information is conflicting regarding the association of systemic and local progestin therapies and increased risk for breast cancer, and these therapies have not been studied in women at high risk for breast cancer. Current recommendations are for shared decision-making with patients regarding local and systemic progestin therapies, especially if the breast cancer is progesterone-receptor positive. Continuous progestin-based systemic therapies such as megestrol and medroxyprogesterone acetate and localized therapies such as the 52-mg levonorgestrel intrauterine device (LNG-IUD) are used to treat endometrial hyperplasia and can be considered for patients who have contraindications to surgery or are interested in future childbearing. Megestrol (40 mg) improves endometrial hyperplasia, but it can have adverse effects.<sup>43</sup> Endometrial hyperplasia regressed in 91.8% of women after 6 months of treatment with depot medroxyprogesterone acetate.<sup>44</sup> Depot medroxyprogesterone acetate, however, can cause weight gain and lower bone mineral density.<sup>45</sup>

The 52-mg LNG-IUD, which delivers 20 mcg of LNG per day, has been studied for both the pre-

vention and treatment of endometrial pathology in women being treated with tamoxifen. Compared with oral progestin therapy, LNG-IUD use leads to higher resolution rates of endometrial hyperplasia without atypia.<sup>46</sup> High-dose local progestins induce profound endometrial suppression through epithelial atrophy, decidualization, and vascular change such that the endometrium becomes unresponsive to ovarian steroidal activity. Multiple studies have confirmed that endometrial hyperplasia and endometrial polyp formation are reduced at long-term follow-up (24–60 months) for LNG-IUD users (Peto odds ratio, 0.13 [95% CI, 0.03–0.66]).<sup>47</sup> The Finnish Cancer Registry study concluded that the LNG-IUD is associated with excess risk for lobular cancer (standardized incidence ratio, 1.33 [95% CI, 1.20–1.46]) and ductal breast cancer (standardized incidence ratio, 1.20 [95% CI, 1.14–1.25]) compared with nonuse.<sup>48</sup> However, LNG-IUD use has much less systemic exposure and could be a relatively safer option than systemic progestin therapies. In a study reviewing the recurrence of breast cancer in LNG-IUD users, risk did not increase for users vs nonusers (adjusted hazard ratio, 1.86 [95% CI, 0.86–4.00]).<sup>49</sup> Currently, many practitioners recommend LNG-IUD as a treatment option for endometrial hyperplasia for premenopausal women who desire to preserve fertility and who are at an increased risk for breast cancer. Additional research is needed in this area with this specific patient population.

Untreated atypical endometrial hyperplasia can progress to endometrial cancer; therefore, hysterectomy is recommended. However, in patients with endometrial hyperplasia due to tamoxifen therapy who want to preserve fertility, tamoxifen should be discontinued. After tamoxifen discontinuation, the risk of endometrial cancer decreases and is the same as for nonusers after less than 3 years of use.<sup>50</sup>

In this case, the patient had a dilation and curettage, hysteroscopy, and polypectomy, and after counseling for risks and benefits, she was prescribed LNG-IUD therapy to reduce the recurrence of hyperplasia. The LNG-IUD can be considered for 12 to 24 months with ongoing endometrial surveillance and monitoring of a patient's menstrual symptoms. Thereafter, tamoxifen could be restarted and continued for 2 additional years. If the patient had a hysterectomy, tamoxifen could be resumed for 2 years, for a total of 5 years of preventive therapy. In addition, when a patient is postmenopausal, she can be counseled regarding use of an aromatase inhibitor as risk-reducing endocrine therapy.

It is important to counsel premenopausal women on the use of tamoxifen, ie, that tamoxifen is a category D medication that can cause fetal anomalies, and barrier contraception is routinely recommended. In addition, barrier contraception should be continued for 2 months after tamoxifen is discontinued.

## Clinical pearls

- Both premenopausal and postmenopausal women receiving tamoxifen who have irregular menstrual bleeding warrant evaluation with pelvic ultrasonography and endometrial biopsy to exclude endometrial pathology.
- Tamoxifen should be discontinued if a patient is diagnosed with endometrial hyperplasia. Short-term use of an LNG-IUD is an option to manage endometrial hyperplasia for women who want to preserve fertility or are not good surgical candidates. Thereafter, tamoxifen can be restarted as preventive therapy with barrier contraception.
- Per National Comprehensive Cancer Network guidelines, tamoxifen can be restarted in patients with tamoxifen-induced endometrial hyperplasia who had a hysterectomy or received LNG-IUD for 2 years in order to manage and treat endometrial hyperplasia.
- A shared decision-making discussion is warranted regarding the use of progestin IUDs because current data do not show an increase in breast cancer risk. A balanced discussion that accounts for the patient's age, medical needs such as contraception or controlling bleeding, and comorbidities is prudent.

## CASE 5

A 56-year-old postmenopausal woman presented to your clinic for her well-woman examination. She was generally healthy, with a body mass index of 29.2. She exercised on the weekends, usually walking for 1 hour, and reported drinking 1 glass of wine with dinner. Her medical history was significant for right breast excisional biopsy for ADH diagnosed 6 years previously. She completed 5 years of risk-reducing endocrine treatment with exemestane. She requested additional information about lifestyle counseling to reduce her lifetime risk for breast cancer.

## Discussion

A healthy lifestyle is associated with a reduced risk for invasive breast cancer, especially in postmenopausal women. Weight gain increases breast cancer risk. Fatty tissue is metabolically active, which can pro-

duce inflammatory markers such as adipokines, and is hormonally active, which can lead to high insulin and estrogen levels. These changes can disrupt cellular repair mechanisms, which can subsequently prompt breast cancer to develop and progress.<sup>51</sup> The Western diet is characterized by consumption of red meat, processed meat, animal fat, and ultraprocessed foods that can ultimately result in a higher body mass index and increased adipose tissue, and, thus, increased estrogen levels. For postmenopausal women, eating a diet low in fat (< 20%), processed meat, and red meat and high in fruits, vegetables, and whole grains can lower the incidence and mortality of breast cancer.<sup>51,52</sup>

Regular physical activity has the most robust effect on breast cancer among all the lifestyle factors, with regular moderate- or high-intensity exercise leading to reduced risk in postmenopausal women. The risk for premenopausal women is reduced with vigorous physical exercise done regularly and sustained over a lifetime.<sup>53</sup> Total physical activity (metabolic equivalent tasks per week) positively influences multiple interrelated biologic factors such as reduced adiposity and increased sex hormone binding globulin, as well as reduced estrogens, androgens, and inflammatory markers, which in turn influence menstrual function.<sup>54</sup> A lifestyle index that included cigarette smoking, physical inactivity, and unhealthy eating showed an inverse relationship to breast cancer.<sup>55</sup> Women with the highest healthy lifestyle score had 44% lower odds of breast cancer than those with the lowest score (odds ratio, 0.56 [95% CI, 0.36–0.88]; *P* for trend = .004).<sup>55</sup>

Even in small amounts, alcohol consumption can increase the risk of breast cancer. The mechanism by which alcohol exerts a carcinogenic effect is unclear but may be related to the effects of alcohol on sex hormones, ie, interference with estrogen pathways and estrogen receptors.<sup>56</sup> Women who consumed 15 g to 30 g of alcohol daily had increased levels of estrogens, androgens, and progesterone. In addition,

acetaldehyde, a metabolite of alcohol, is mutagenic because it inhibits the repair of carcinogen-induced DNA damage. The National Institute on Alcohol Abuse and Alcoholism classifies a standard drink as having 14 g of alcohol (12 oz of beer, 5 oz of wine, 1.5 oz of distilled spirits). Consuming too much alcohol can negatively affect the absorption of dietary nutrients that have anticarcinogenic properties, eg, folate, beta carotene, lutein, and zeaxanthin.<sup>57</sup>

Tobacco use also affects lifestyle and risk of breast cancer.<sup>58</sup> Polycyclic aromatic hydrocarbons and tobacco-specific nitrosamines are the most well-known carcinogens; the DNA adducts they produce can circumvent cellular repair mechanisms and cause genetic variations. In pooled data from 14 cohort studies, smoking for more than 10 years before the first childbirth increased the risk of breast cancer by 18% compared with women who never smoked.<sup>59</sup>

### Clinical pearls

- Current American Cancer Society guidelines recommend achieving and maintaining a healthy weight and limiting alcohol intake and avoiding smoking to reduce cancer risk. Individually tailored whole foods, plant-based dietary patterns, and 150 to 300 minutes of moderate intensity or 75 to 150 minutes of vigorous intensity activity each week (or a combination of these) also reduce breast cancer risk.
- Women should be made aware of the considerable decrease in breast cancer risk with healthy lifestyle choices.

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