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Association Between Lifestyle Changes, Mammographic Breast Density, and Breast Cancer

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Abstract

In screening for breast cancer (BC), mammographic breast density (MBD) is a powerful risk factor that increases breast carcinogenesis and synergistically reduces the sensitivity of mammography. It also reduces specificity of lesion identification, leading to recalls, additional testing, and delayed and later-stage diagnoses, which result in increased health care costs. These findings provide the foundation for dense breast notification laws and lead to the increase in patient and provider interest in MBD. However, unlike other risk factors for BC, MBD is dynamic through a woman's lifetime and is modifiable. Although MBD is known to change as a result of factors such as reproductive history and hormonal status, few conclusions have been reached for lifestyle factors such as alcohol, diet, physical activity, smoking, body mass index (BMI), and some commonly used medications. Our review examines the emerging evidence for the association of modifiable factors on MBD and the influence of MBD on BC risk. There are clear associations between alcohol use and menopausal hormone therapy and increased MBD. Physical activity and the Mediterranean diet lower the risk of BC without significant effect on MBD. Although high BMI and smoking are known risk factors for BC, they have been found to decrease MBD. The influence of several other factors, including caffeine intake, nonhormonal medications, and vitamins, on MBD is unclear. We recommend counseling patients on these modifiable risk factors and using this knowledge to help with informed decision making for tailored BC prevention strategies.

Key words: breast cancer; breast density; breast health; exercise; hormone therapy; nutrition.

Implications for Practice

Higher breast density is a known risk factor for breast cancer. Lowering mammographic breast density can improve the quality of mammograms, thereby reducing recalls and additional unnecessary testing. Alcohol consumption and menopausal hormone therapy (MHT) directly influence breast density and the development of breast cancer. Women planning to initiate MHT should be counseled on this influence on breast density and mammograms. Other lifestyle factors such as smoking, a sedentary lifestyle, and increased body mass index increase the risk of breast cancer through pathways other than altering breast density, but women should be counseled on these risk factors to reduce their lifetime risk for breast cancer.

Introduction

Case Vignette

A 53-year-old woman presents to the office after she has completed her screening mammography and received a letter stating that the results are benign, but both breasts are extremely dense. Since density can obscure small masses, she is advised to discuss the results with her health care professionals. She is nulliparous with no family history of breast cancer (BC) and has never used menopausal hormone therapy (MHT). Her last menstrual period was 2 years ago; her body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) is 23.1. She drinks 1 glass of wine daily and has a sedentary lifestyle. She is a nonsmoker and eats a "regular American diet" that includes a high intake of red meat and processed foods. Because she started to experience bothersome menopausal symptoms, she is contemplating MHT.

She is wondering whether her lifestyle factors or MHT would affect breast density and whether she could modify her lifestyle to decrease breast density. How would you counsel her?

Mammographic Breast Density and BC

Mammographic breast density (MBD) is a radiologic estimate of the amount of radiopaque or highly dense breast tissue composed of epithelial and stromal elements compared with the amount of radiolucent or low-density fatty tissue. Fatty tissue appears dark or radiolucent because it absorbs fewer X-rays, whereas epithelial and stromal elements appear white or radiopaque because they filter X-rays efficiently and absorb more energy. The Breast Imaging Reporting and Data System (BI-RADS), developed by the American College of Radiology, provides

standardized communication tools for radiologists and classifies breast density into 4 groups depending on the amount of fibroglandular tissue in relation to fatty tissue: entirely fatty (category *a*); scattered fibroglandular (category *b*); heterogeneously dense (category *c*); and extremely dense (category *d*).[1] In approximately 50% of mammography reports in the US, breast tissue is reported as heterogeneously dense or extremely dense, and dense breast tissue is the most prevalent risk factor for BC.[2] Breasts classified as BI-RADS category *a* or *b* are generally referred to as *low-density breasts*, whereas breasts in category *c* or *d* are referred to as *high-density breasts*.[1]

We acknowledge that definitions and quantification of breast density are heterogenous and at times subjective, with interreader and intrareader variability, which makes comparisons between studies and institutions challenging. While this variability can be decreased with the use of computer-based assessments that use software programs to extract data from digitized mammograms for quantitative analysis, these products are not available at all institutions since observer-based scoring tends to be more cost-effective.[1,3,4] With the mandatory reporting required by dense breast notification laws, more women are aware of their breast tissue density and are questioning their health care professionals about MBD and lifestyle modifications for improving MBD.[5]

Clinical Impact of MBD Changes and BC

Considerable changes in breast tissue occur throughout a woman's life, with expansion and development of the mammary gland during the pubertal years, proliferation and involution during the menstrual cycles, glandular and ductal changes during lactation, and postmenopausal fatty deposition and involution after menopause, so that MBD is subject to changes.[6] Like some other modifiable risk factors for BC, MBD has the potential to be modified over the course of a lifetime.[7,8]

Are There Any Benefits to Modifying MBD?

The *masking effect* refers to situations where dense breast tissue obscures small, underlying breast lesions that have a mammographic attenuation similar to fibroglandular tissue (ie, isodense). With this lack of contrast, mammographic interpretation of dense breast tissue is challenging, and small noncalcified BC can be overlooked and lead to larger tumors with lymph node involvement and decreased survival rates.[9] Mammography has an overall sensitivity of 70%-90% and a sensitivity of 80%-98% among women with category *a* breast density; however, the sensitivity can be as low as 30%-48% for women with category *d* breast density.[10,11] Reducing MBD helps to decrease the masking effect, thereby improving the sensitivity of mammograms and facilitating an earlier diagnosis.

The fact that MBD is a modest and independent risk factor for BC has been reproduced in large-cohort, case-control, and population-based studies.[12-14] BC is 4-6 times more likely to develop in women with breast density in category *d* than in women with breast density in category *a*.[13,15] The biologic mechanisms by which MBD contributes to increased BC are not known.[16] Although therapeutic interventions to reduce MBD, such as aromatase inhibitor therapy and selective estrogen receptor blockers, are known to reduce BC risk, their continual use over a lifetime is not feasible.[17] MBD reduction is a marker for their efficacy and in general can be an effective strategy to reduce a woman's lifetime risk of BC, but additional research is needed.

Risk Factors for BC

Risk factors for BC include nonmodifiable factors such as genetics and reproductive factors (eg, age at menarche, age at menopause, parity, and age at first live birth).[7,8,18,19] This article reviews the influence of prevalent and modifiable lifestyle factors, such as alcohol, diet, physical activity, smoking, BMI, and medications that affect MBD, and their effects on BC risk.

Does Alcohol Intake Influence MBD?

In a systematic review of multiple studies with over 70 000 participants, an increase in MBD was found to be associated with alcohol intake.[20] A biologically plausible mechanism for this association is an increase in estrogen production and aromatase enzyme activity, which facilitates peripheral conversion of androgens to estrogens, thus causing increased estrogen levels.[20] Alcohol also increases insulin growth factor and insulin-like growth factors, which can cause proliferation of mammary epithelial cells and work synergistically with estrogen, leading to increased MBD.[20,21]

In a cross-sectional study involving 424 premenopausal and postmenopausal women, alcohol intake of more than 10 g daily (25 g in 250 mL of wine; 12 g in 300 mL of beer; and 6.2 g in 20 mL of distilled spirits) was associated with increased MBD.[22] In the Minnesota Breast Cancer Family cohort study with a sample size of 1508 premenopausal and postmenopausal women, MBD increased in women with daily alcohol consumption of 3.9 g or less compared to never drinkers ($P = .08$).[23] In a cross-sectional study involving 497 women with high breast density and 288 women with low breast density, breast density increased significantly ($P = .009$) with increasing alcohol consumption when women classified as heavy drinkers (≥140 g weekly) were compared with women classified as nondrinkers (odds ratio [OR], 2.1; 95% CI, 1.2-3.9; $P = .01$).[24] Similarly, a longitudinal study involving around 2000 European women demonstrated a positive association between alcohol consumption and increased breast density ($P = .01$).[25] In the Danish Diet, Cancer, and Health study, which was a large cohort study involving 5356 women, MBD was higher among women aged 20-29 years who consumed more than 7 drinks per week, especially if the drinks were distilled spirits (OR, 1.31; 95% CI, 1.00-1.72).[26] However, the results of these studies should be interpreted with caution because the increase in MBD may have been influenced by other concurrent risk factors.[27]

Alcohol is a known risk factor for BC, particularly estrogen receptor-positive cancer, and alcohol increases MBD in premenopausal and postmenopausal women.[25,26] Increased MBD could be a mechanism of carcinogenic potential.

Does Dietary Pattern Influence MBD?

Data regarding the role of dietary fat on MBD are generated mostly from observational studies and are equivocal and inconsistent.[28,29] In a follow-up study of 230 adolescents who were randomly assigned to a low-fat diet, MBD did not change between the groups.[30] However, in the Minnesota Breast Cancer Family cohort study involving 1508 women, the intake of saturated fat and dairy products was associated with decreased MBD in premenopausal women.[23]

The Mediterranean diet and its role in decreasing MBD and the incidence of BC have been investigated. A cross-sectional study involving 424 women showed an inverse association between consumption of the Mediterranean diet and MBD.[22] Furthermore, the diet, physical activity, and mammography (DAMA) trial involved 424 postmenopausal women randomly assigned to 1 of 4 treatment interventions (diet, physical activity, diet and physical activity, and control) to assess for change in the percentage of MBD.[31] The dietary intervention consisted of plant-based foods with low glycemic load and low level of saturated fats. Both the dietary and the physical activity intervention groups demonstrated a modest decrease in percentage breast density compared to controls. In the European Prospective Investigation into Cancer and Nutrition (EPIC) Florence longitudinal study, diets with high carbohydrate intake and high glycemic load were found to be associated with an increased MBD.[32] High glucose levels lead to hyperinsulinemia and subsequent activation of insulin receptors and elevated insulin-like growth factor 1, which works synergistically with estrogens to cause proliferation of mammary epithelium and, hence, increased MBD.[32]

Does Caffeine Intake Influence MBD?

While some epidemiologic studies have suggested that the risk of BC decreases with caffeine intake, studies of caffeine intake and its role on MBD are limited and inconsistent. Data for the cohorts in the Nurses' Health Study and the Nurses' Health Study II showed that among premenopausal women there was no association between caffeine intake and MBD, but MBD did increase with the consumption of 2 or more cups of decaffeinated coffee daily ($P = .03$).[33] Among postmenopausal women, an inverse association was noted for both decaffeinated coffee consumption and total coffee consumption with percentage breast density ($P = .04$).[33] These data were extrapolated from 4130 cancer-free women who filled out questionnaires preceding the dates of their mammograms.[33] Caffeine can alter estrogen metabolism, thus decreasing circulating estrogen levels, and caffeine has potential antioxidant properties that could lead to lower MBD.[33] Further studies are needed to clearly define the role of caffeine intake on MBD.

Does Aerobic Exercise Influence MBD?

Various studies have attempted to evaluate potential associations between physical activity and MBD. In a prospective cohort of 5,703 Danish women, no association was noted between physical activity and MBD.[34] The Alberta Physical Activity and Breast Cancer Prevention (ALPHA) trial randomly assigned 320 postmenopausal women to an exercise arm (45 minutes on 5 days weekly) or a control arm for 1 year to assess whether aerobic exercise influenced baseline MBD; the study found that while there was a protective effect of exercise on BC risk, there was no significant change in MBD between the groups.[35] Alternatively, the DAMA trial demonstrated a moderate reduction in MBD in women randomly assigned to the physical activity intervention arm when compared to controls.[31]

A large systematic review published in 2012 assessed the relationship between physical activity and MBD by analyzing and comparing 20 studies that addressed this topic; the conclusion was that there was no compelling evidence of an association between physical activity and MBD.[36] This lack of effect on MBD could be explained by the fact that physical activity affects only the fatty portion of the breast and not the fibroglandular area. On the basis of the current data, although physical activity decreases the risk of BC, the mechanism is likely mediated through a pathway other than an influence on MBD.

Does Smoking Influence MBD?

Tobacco smoking has an antiestrogenic effect because it enhances the metabolism of estradiol to metabolites with minimal estrogen activity at the receptor sites.[37-39] In addition, it leads to decreased estrogen levels through (1) increased hepatic metabolism of estradiol by induction of cytochrome P450 enzymes and increased sex hormone–binding globulin levels and (2) decreased bioavailability due to inhibition of aromatase enzyme activity.[37,40]

Several studies have shown an inverse relationship between smoking and MBD. In a case-control study with 203 women in each group, current smokers, compared to nonsmokers, were less likely to have a high-risk mammographic parenchymal pattern (OR, 0.37; 95% CI, 0.14-0.94).[41] In a cross-sectional cohort study, MBD was lower by 7.2%, which was statistically significant, in both premenopausal and perimenopausal women who were current smokers compared to never smokers.[39] Results of a cross-sectional study of postmenopausal women showed that the adjusted mean percentage breast density was significantly lower for current and former smokers ($P = .003$) compared to never smokers ($P = .006$).[42] In the Danish Diet, Cancer, and Health cohort consisting of 5356 women, the association between MBD and smoking was strongest among women who began to smoke when they were younger than 16 years, smoked at least 15 cigarettes daily, had a smoking history of at least 5 pack-years, smoked for at least 30 years, and smoked for at least 11 years before their first childbirth.[43] In a large population-based cohort study involving 23 456 women, tobacco use was found to be inversely associated with percentage breast density and positively associated with nondense area, which is predominantly adipose tissue.[44] These findings support a mechanism whereby smoking increases adipose tissue in the breast and results in decreased MBD. No association has been found between passive smoking and MBD in other cohort studies.[43,45]

Smoking has been associated with an increased risk of BC; however, smoking-related carcinogens may increase BC risk through pathways that do not involve increasing MBD because smoking seems to be inversely associated with MBD. Future studies are needed to understand the mechanisms and underlying biology between smoking and BC to enable better preventive interventions.

Does BMI Influence MBD?

The influence of birth weight on MBD is unclear. Among premenopausal women, an equivocal association exists between MBD and elevated BMI in early life; however, for postmenopausal women, an inverse association exists.[46] BMI has been found to be negatively associated with the dense area and percentage breast density while being positively associated with nondense area.[47,48] In an observational study that included 573 women undergoing definitive BC surgery and used mammography and magnetic resonance imaging to assess breast tissue characteristics, women with a BMI of 25 or more had lower MBD ($P < .0001$) and less fibroglandular tissue ($P < .0001$) but higher background parenchymal enhancement (BPE) ($P = .005$).[49] BPE varies with the vascularity of the fibroglandular tissue and is hormonally sensitive.[50,51] Elevated

BPE may indicate a potential mechanism that increases the BC risk for women with overweight or obesity.

In multiple cohort studies of women who had bariatric surgery, women with category *a* breast density seemed to have an increase in MBD with weight loss, potentially because of an overall decrease in breast adipose tissue compared to a relatively modest decrease in fibroglandular tissue.[52,53] Women with category *b* or *c* breast density did not show significant density changes even with marked weight loss. According to a large meta-analysis of 13 case-control studies, the percentage of dense breast, which is the ratio of fibroglandular tissue to fatty tissue, appears to be a greater risk factor than the absolute amount of dense breast tissue.[54]

BMI and MBD are inversely related to each other and are independent risk factors for BC, which suggests that MBD and obesity may have alternative pathways in elevating the risk of BC.[47,55-57]

Influence of Medications on MBD

Does MHT Influence MBD?

While prolonged use of MHT with progestins is known to slightly increase the incidence of BC, limited data exist regarding an association between combined hormonal contraceptives and MBD. In an analysis of 3 case-control studies of premenopausal women who used combined hormonal contraceptives (compared with those who did not), and who later had BC, MBD changes were not significantly different.[58]

In the Women's Health Initiative randomized trial of 16 608 postmenopausal women, an increase in MBD was seen in the estrogen-progestin group after 1 and 2 years of follow-up.[59] Compared to women randomly assigned to receive a placebo, women in the MHT group had the greatest mean increase from baseline in MBD during the first year (6% increase vs. 0.9% decrease in the placebo group) and a smaller increase during the second year (4.9% increase vs. 0.8% decrease in the placebo group).[59] In the postmenopausal estrogen/progestin interventions (PEPI) trial, all 3 groups of women randomly assigned to receive combinations of conjugated equine estrogen and progestin had a statistically significant increase (3%-5%) in MBD over 12 months when compared to the placebo group.[60] An observational population-based cohort study consisting of 5212 postmenopausal women who used a combination estrogen-progestin regimen showed an increase in MBD, compared to nonusers, which was maintained with continued use of MHT.[61] MBD increased with MHT most notably in the first year and in current users and decreased to baseline after MHT was discontinued.[61,62] A prospective study comparing various MHT regimens showed a significant increase in MBD for the continuous estrogen-progestin group compared to both cyclic estrogen-progestin and estrogen-only groups ($P < .001$).[63] A dose-response relationship was identified with the progestin dosage.[63]

Fornili et al[64] described an association between MHT, MBD, and BC risk limited to hormone receptor–positive BCs only. No association was found between MHT and hormone receptor–negative BCs. The adjusted OR of BC for current MHT users compared to never users was 1.67 (95% CI, 1.04-2.68). According to this study, increased MBD contributed up to 50% of the influence of MHT on an increased risk for hormone-positive BC.

A limited number of studies have investigated the role of androgens such as testosterone and dehydroepiandrosterone (DHEA) and DHEA sulfate on MBD, but most studies have shown no significant influence. A randomized double-blind controlled trial consisting of 250 women found no change in MBD after 1 year between postmenopausal women receiving transdermal testosterone and women receiving placebo, but circulating levels of androgens were not statistically significantly different after adjusting for BMI.[65] In another randomized controlled study, the addition of transdermal testosterone to postmenopausal women receiving estrogen-progestin therapy (compared to women receiving placebo) did not change MBD after 6 months of therapy.[66]

Can Nonhormonal Medications Influence MBD?

Hyperinsulinemia through exogenous insulin administration has been implicated as a possible risk factor for BC because it stimulates cell proliferation in human cancer cell lines[67] and normal breast tissue.[68] Increased insulin levels were associated with increased MBD in the Danish diet, cancer, and health cohort consisting of 5644 women.[69] Observational studies and analyses have associated metformin with a lower risk of BC in postmenopausal women[70,71] owing to its antiproliferative effect on breast tissue resulting from a decrease in the circulating levels of insulin, androgens, and estrogen.[72,73] In 2 small observational studies of postmenopausal women with type 2 diabetes, an inverse relationship was identified between the use of metformin and MBD, but the relationship was not statistically significant.[74,75] Use of fertility drugs and statins was reviewed and not shown to be associated with significant changes in MBD.[76-78]

Limited and mostly observational data are available on the association of supplements and MBD. Studies reviewing the association with vitamins B_{12}, C, E, and D show conflicting results.[23,79] Vitamin D may be involved in inhibiting the proliferative pathways of insulin-like growth factor 1 and estrogen, by downregulating its receptors and thus decreasing MBD, but studies on the influence of vitamin D on MBD have been inconclusive, and results should be interpreted with caution owing to study design and potential confounders.[79-81]

Case Vignette Response

The patient should be made aware that MBD is an independent risk factor for BC but should be reassured that BC does not develop in many women who have dense breast tissue. Because MBD reduces the sensitivity of mammography, she should be counseled about the risks and benefits of supplemental BC screening for informed decision making. She should be commended on her current efforts to avoid smoking and maintain a normal BMI. She should also be counseled about the increase in MBD and BC risk with alcohol use and advised to limit her alcohol intake. Even though physical activity and diet do not seemingly have a direct influence on MBD, she should be counseled on initiating an exercise program that incorporates a minimum of 150 min of aerobic exercise per week and adopting a Mediterranean diet, which reduces cardiovascular disease and BC risk. Since she has bothersome vasomotor symptoms, without any contraindications, she is an ideal candidate for MHT; she should be counseled that MHT increases MBD, which can further reduce the sensitivity of mammography, and she should also be reassured that when MHT is discontinued, MBD returns to baseline. Table 1 summarizes the effects of these lifestyle

Table 1. Lifestyle factors that affect MBD and risk of BC.

Lifestyle factor	Effect on MBD[a]	Effect on BC risk[a]
Alcohol use	↑	↑
Mediterranean diet	↔	↓
Physical activity	↔	↓
Smoking	↓	↑
Elevated BMI	↓	↑
Menopausal hormone therapy	↑	↑

[a] Arrow pointing up indicates increased effect; arrow pointing down, decreased effect; double horizontal arrow, no effect.
Abbreviations: BC, breast cancer; BMI, body mass index; MBD, mammographic breast density.

factors. Other risk factors and their influence on MBD require further studies because the data are conflicting.

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Conflict of Interest

The authors indicated no financial relationships.

Author Contributions

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Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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