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Mammographic breast density, endocrine therapies, and breast cancer risk

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The breast is composed of 3 main tissues: fat, fibrous/connective tissue, and epithelial tissue. Differences in the relative amount of these tissues result in variability between individuals in the radiologic appearance of the breast on the mammogram. Fat is radiolucent and appears dark on the mammogram, whereas epithelium and connective tissue are radio-dense and appear light on the mammogram.¹ Mammographic breast density (MBD) reflects the appearance

of the breast on the mammogram and indicates the relative proportion of radiographically dense, ie, white or light areas, of the breast.

MBD categories

Several classification schemes have been used to categorize MBD over the decades. The earliest categorization was Wolfe's parenchymal pattern that classified the extent and type of density into 4 categories²:

- N1: Nondense, no ducts visible;
- P1: Prominent ductal pattern occupying less than one-fourth of the breast;
- P2: Prominent ductal pattern occupying more than one-fourth of the breast; and
- DY: Homogenous, plaque-like areas of density.

Currently, the most common clinical measure of density is the Breast Imaging Reporting and Data Systems (BI-RADS) density method, proposed by the American College of Radiology.³ BI-RADS density is a subjective measure used by radiologists to classify a mammogram as follows:

- D1: Fatty;
- D2: Scattered density;

- D3: Heterogeneously dense; or
- D4: Extremely dense.

Computer-assisted methods are used to estimate quantitative measures of MBD, including percent density (percentage of the overall breast showing dense tissue; PD), absolute dense area, and nondense area.^{4,5}

MBD and breast cancer risk

Elevated MBD is considered one of the strongest risk factors for breast cancer regardless of whether it is assessed as a categorical or quantitative measure.⁶ Women in the highest categories of breast density have a 4- to 6-fold increased breast cancer risk compared with women in the lowest categories. MBD has been shown to be a stronger risk factor for breast cancer than any others except age and genetic mutations.⁶

The association between MBD and breast cancer has been seen both in older and younger women undergoing screening mammograms, as well as in Caucasian and non-Caucasian populations.^{4,6,7}

Hormonal influence on MBD

There is strong and consistent evidence that MBD is influenced by

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FROM THE EDITOR

Nanette F. Santoro, MD



Searching for lost car keys

There is an anecdote about a drunk, muttering to himself about losing his car keys after leaving a bar. A friend finds him on his hands and knees under the streetlight across the street from both the bar and his car, unable to find his keys (probably a good thing, given the circumstances). The friend points out the futility of looking for his lost keys across the street from his car, to which the drunk replies, "Yes, I know, but the light is much better over here!"

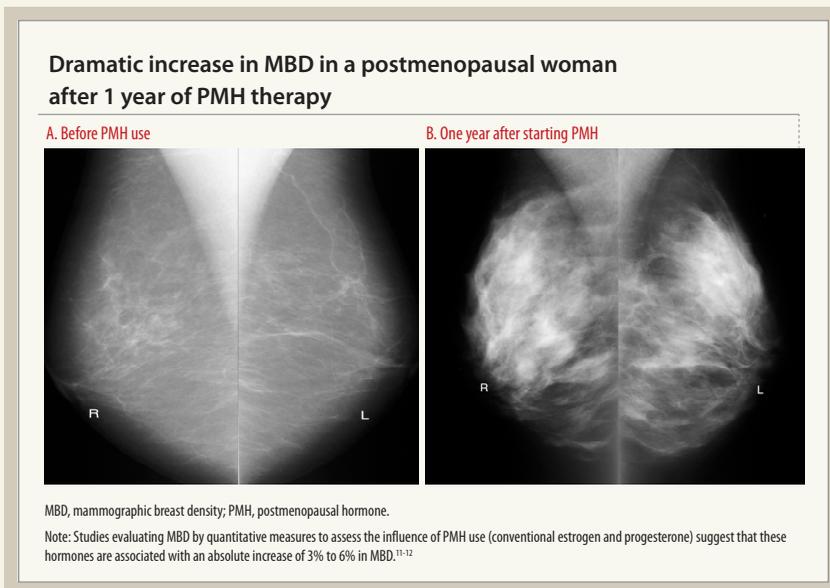
By coincidence, this issue of *Menopausal Medicine* addresses a topic that is presently a firestorm of controversy¹⁻³: breast cancer risk, detection, and screening. This past fall, Dr Laura Esserman, a renowned breast surgeon from San Francisco, published an insightful commentary on the state of breast cancer screening.⁴ In it, she and her coauthors provide insight into why mammography screening has not lived up to its expectations in terms of mortality prevention, and they make recommendations to tackle this problem at a fundamental level.

For those of us who practice obstetrics/gynecology, the story of the Pap smear has been a signature success of cancer prevention.⁵ Unlike breast cancer, cervical cancer follows a relatively indolent course in most cases. Unlike the breast epithelium, cervical epithelium is available for biopsy and direct visualization without a need for skin incision. To make matters even more favorable, precancerous lesions are readily amenable to complete excision. Arguably, the success story of the Pap smear has informed our approach to the prevention of breast cancer and has led us to a state of inappropriate optimism and faith in the screening test.

Unlike cervical cancer, there appears to be more variation in the rate of growth of breast tumors. Some tumors can go from undetectable to metastatic within a single screening interval.⁴ These more aggressive tumors tend to occur in younger women, and make annual mammographic screening in women in the age group of 40 to 50 considerably less cost-effective. This age group has always been a controversial one in terms of mammography screening guidelines, initiation of screening, and follow-up interval, with different experts making somewhat different recommendations over the years. In Esserman's analysis, she discusses the fact that for both breast and prostate cancer, there has been less benefit than expected from mass screening paradigms. This is because low-grade lesions that will not cause death—and, in some cases, may even spontaneously regress⁶—are detected admirably well and excised, whereas the aggressive lesions, which are not "playing by the rules" we have learned with Pap smear screening, become metastatic in less than one screening interval and bedevil attempts at clinical detection. These more aggressive cancers are not decreasing at a rate that unequivocally justifies annual mammography for half of the population. The data lead us to the conclusion that the typical preventive cancer screening model that

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hormonal factors such as menopause, age at menarche, parity, age at first birth, and use of exogenous hormones.^{8,9}

The influence of exogenous hormones on MBD is best illustrated by positive associations of MBD with postmenopausal hormone (PMH) therapy and inverse associations with tamoxifen, as described below. These associations are important because they suggest interindividual variability in response to hormone therapies manifested in MBD changes, which may translate into differential breast cancer risk.

Influence of PMH

With estrogen depletion during menopause, the breast glandular tissue undergoes regression.¹⁰ This is also reflected by a decrease in MBD during and after menopause.

What happens to breast tissue when this process is interrupted by PMH? When assessing the influence of conventional estrogen-plus-progesterone PMH use, studies evaluating MBD by quantitative measures suggest that these hormones are associated with an absolute increase of 3% to 6%

in MBD.^{11,12} The **FIGURE** illustrates one woman's dramatic change in MBD after 1 year of PMH use.

In the Norwegian Breast Cancer Screening Program (n = 1007), current users of PMH therapy had a significantly higher mean percent MBD than never users (MBD, 11.5 (9.7-13.7) for current users vs 7.2 (6.6-7.8) for never users; *P* for trend <.001).¹³

In the Women's Health Initiative (WHI) study, women were randomized to receive daily combined conjugated equine estrogens (CEE, 0.625 mg) plus medroxyprogesterone acetate (MPA, 2.5 mg) or placebo. Combined PMH (n = 202) was associated with an absolute increase of 6.0% in MBD at 1 year compared with baseline, whereas the placebo group (n = 211) had a decrease of 0.9% in density (a 6.9% difference between the treatment and placebo groups).¹¹ More than 75% of women on active PMH had an increase in MBD.

Similarly, the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial, which examined the association between PMH and MBD, also saw increases with combined hormone therapy.¹² Women were randomized to 1 of 5 interventions: (1) placebo (n = 112);

(2) CEE, 0.625 mg/d (n = 114);(3) CEE + cyclic MPA, 10 mg/d for 12 d/mo (n = 109); (4) CEE + daily MPA, 2.5 mg/d (n = 121); or (5) CEE + micronized progesterone (MP), 200 mg/d for 12 d/mo (n = 115). The mean changes in percent MBD over 12 months were statistically significantly greater for all combined therapy regimens relative to women in the placebo group (range, 3.1%-4.8%), although women in the estrogen-alone arm showed no significant change in MBD (1.17%, 95% confidence interval [CI], -0.28-2.62; *P* = .24). Moreover, there was no significant difference between the change in MBD with the type of progestin or pattern of progestin use for cyclic or continuous MPA (CEE + cyclic MPA, 4.8%; CEE + continuous MPA, 4.6%; and CEE + MP, 3.1%).¹²

Taken together, these studies suggest that estrogen-and-progestin combined therapies at conventional doses are associated with increased breast density, regardless of the pattern of progestin administration. And, importantly, the associations of these therapies with MBD change parallel the associations with breast cancer risk, such that there are increases in breast cancer with combination therapy but not with estrogen alone.¹⁴

Although lower-dose regimens are hoped to have less influence on breast density, a recent study found no difference between the associations of conventional and low-dose hormone therapy with MBD.¹⁵ Importantly, Buist et al reported that 1 to 2 months of cessation of PMH use was associated with only small decreases in MBD, and stopping therapy for this short period did not affect mammogram recall rates.¹⁶

Influence of tamoxifen, raloxifene, and aromatase inhibitors on MBD

In view of the positive association between PMH and MBD, the logical

question is whether tamoxifen, raloxifene, or aromatase inhibitors reduce MBD.

Tamoxifen is a selective estrogen receptor modulator (SERM) that competitively binds to estrogen receptors and blocks estrogen synthesis.¹⁷ The antiestrogenic influence on the breast resulted in its use as adjuvant endocrine therapy for women with estrogen receptor-positive postmenopausal breast cancer. Tamoxifen has also been used as a chemopreventive agent to reduce the risk of breast cancer in women at high risk. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) randomized clinical trial of high-risk women, 5 years of tamoxifen therapy was shown to reduce invasive breast cancer risk by 49% and noninvasive breast cancer risk by 50% compared with placebo.¹⁸

Several studies have examined the effect of tamoxifen on MBD¹⁹⁻²² using different estimation methods for MBD and study populations (ie, women with known breast cancer on adjuvant tamoxifen or women at high risk for breast cancer on tamoxifen for chemoprevention). These studies have consistently demonstrated that women on tamoxifen do experience a statistically significant reduction in MBD. Some of these studies noted that decreases in percent MBD occurred at a greater frequency in premenopausal than in postmenopausal women.¹⁹

Son et al²¹ demonstrated that 87% of premenopausal women with breast cancer had a decrease in parenchymal area with tamoxifen use, whereas 29% of postmenopausal women experienced a decrease.

Similarly, in the Brisson study,¹⁹ 67% of high-risk women on tamoxifen who were under age 50 experienced a decrease in parenchymal pattern classification compared with 13% of postmenopausal women age 50 or older.

Brisson et al also showed that the magnitude of the decrease in density with tamoxifen therapy was greater in younger women than in older women (-12.1% [SD, 11.0%] in women under age 50 compared with -5.7% [SD, 12.6%] in women age 50 and older).¹⁹

In their study of premenopausal breast cancer cases, Ursin et al⁴ showed that 80% of women experienced a decrease in MBD. However, not all studies saw differences between pre- and postmenopausal women.²²

Because a similar dose of tamoxifen (20 mg/d) was used across studies, it was not possible to evaluate dose response with MBD change. Common to all of these studies was the fact that not all women on tamoxifen experienced a reduction in breast density with therapy; the proportion of women experiencing a reduction in density ranged from 21% to 80%.

This was seen across studies with varying MBD estimation methods, populations (whether high-risk women or cancer cases), and as noted above, varying menopausal status. This suggests the hypothesis that decreases in MBD induced by tamoxifen in a portion of women have clinical significance, resulting in fewer incident cancers among high-risk women and fewer instances of breast cancer recurrence or contralateral events among cases. These women stand to benefit by remaining on tamoxifen. In contrast, those who see little reduction or even increases in MBD may be those who would benefit from alternative treatment approaches.

Raloxifene, another SERM agent, has been used for chemoprevention of breast cancer due to the demonstrated reduction in risk of invasive breast cancers after 5 years of therapy.²³ Some studies have shown similar decreases in MBD among women on raloxifene vs placebo,²⁴ whereas others have

shown small changes in MBD with raloxifene use.¹⁵

In a study of raloxifene and MBD assessed as volumetric breast density from full-field digital images, Eilertsen et al¹⁵ showed a small reduction in volumetric MBD in the raloxifene group (median, -4.1%; 95% CI, -6.9%-2.1%), compared with an increase in MBD seen in the low-dose PMH group (median, 15.0%; 95% CI, 4.8%-28.6%; $P < .0001$).

Aromatase inhibitors (AIs) block local synthesis of estrogen in extracts of human breast tumors²⁵ and currently are the most efficacious endocrine therapy for estrogen receptor-positive postmenopausal breast cancer.

A few studies have examined the association between the AI, letrozole, and MBD, with mixed results. These include a study of 106 postmenopausal women who were randomized to either letrozole or placebo after 5 years of tamoxifen; this study found no difference between the 2 groups in change in MBD after 9 to 15 months.²⁶ Two additional studies examined the influence of letrozole on MBD among postmenopausal women taking PMH: one found no change in percent MBD among 42 high-risk women on either estrogen alone or combination PMH (estrogen and progestins) after taking 2.5 mg letrozole per day for 6 months,²⁷ whereas the other study found a reduction among women on low-dose combination therapy who were taking letrozole (2.5 mg) 3 times weekly for a median of 24 (range, 2-63) months (6.8% vs 1.4% reduction).²⁸

The inconsistent findings of studies of raloxifene and aromatase inhibitors with MBD may be related to the fact that these therapies are used only in postmenopausal women with lower baseline MBD, making small changes hard to detect. However, larger studies with well-calibrated density measures

and follow-up for breast cancer are needed to determine whether MBD can be used as a biomarker for these and other endocrine therapies.

MBD as a clinical marker for breast cancer risk

How can this information be translated to the clinical care of our patients? Studies have recently incorporated the BI-RADs and quantitative MBD measure into breast cancer risk prediction models, which has shown some improvement in risk prediction (improvement c-statistic by 0.01 to 0.06).²⁹ An enhanced model with an MBD measure is, therefore, preferable to the currently existing Gail model but remains poor for individualized risk. Also, it is important to recognize the clinical challenges associated with evaluating mammograms of women with increased MBD, including the need for repeat mammograms and breast biopsies and the difficulty of detecting clinically significant abnormalities.³⁰

Given the associations between exogenous hormones and a change in MBD, a natural question is whether a change in MBD is a potential marker for risk. In other words, if women experience increased MBD with PMH use, are they at greater risk for breast cancer than women who decrease or maintain MBD while on PMH? Or, if

a woman on adjuvant tamoxifen decreases MBD, does this mean that she will have a reduced risk of recurrence compared with a woman who has no change in MBD while on tamoxifen?

Cuzick et al reported the first study to address this question, using women from the IBIS-1 trial, a clinical trial randomizing high-risk women to tamoxifen or placebo and following them over time for breast cancer events.³¹ Mammograms were examined at study entry and at 12 to 18 months for 120 participants who developed breast cancer over the course of the trial and 945 matched controls who did not. MBD was assessed visually by an expert radiologist as a percent of the total breast area. Compared with the placebo arm, women on tamoxifen with $\geq 10\%$ reduction in MBD had lower breast cancer risk (odds ratio [OR], 0.37; 95% CI, 0.2-0.69; $P = .002$), whereas women on tamoxifen with $< 10\%$ reduction in breast density showed no decrease in risk (OR, 1.03; 95% CI, 0.66-1.61; $P = .89$).

These data suggest that change in MBD could be a biomarker for breast cancer risk reduction for women undergoing chemoprevention strategies and could allow for earlier identification of women who would not benefit from tamoxifen therapy. Studies are also under way to examine the influence of change in MBD with PMH use

on breast cancer risk, and results are expected soon. At this time, it is not clear whether the resulting increases and decreases in MBD with endocrine therapies simply change the ability to detect new breast cancers or relate to the pathophysiology of the breast cancer. Additional work is needed to improve our understanding of agents that contribute to change in MBD and their association with breast cancer. Also, the development of reproducible and well-calibrated density measures that can accurately measure MBD are needed to allow for comparability of MBD change across studies and therapy types.

Summary

Understanding variability in the response to endocrine therapies is important so that the most effective therapy can be administered to patients in a timely manner. This includes the administration of exogenous estrogens to healthy women to reduce postmenopausal symptoms as well as breast cancer treatment for women with disease. MBD may contribute to our understanding of interindividual variability in response to therapy. This information can then translate to the clinical setting to facilitate personalized decision-making regarding options for breast cancer treatment and risk-reduction strategies. ⁿ

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we embrace may be a flawed ideal. Thus, while we live in an era where improved breast cancer treatments have led to a 14% increase in 5-year survival (from 75% to 89% from 1975 to 2003⁷), are we really helping our patients by recommending annual screening beginning at age 40? Or are we simply generating more biopsies, sleepless nights, and overdiagnoses? Isn't there a better way?

In November, the US Preventive Services Task Force (USPSTF) published its newest guidelines for breast cancer screening,⁸ an update of the 2002 guidelines⁹ (TABLE). These new guidelines were the equivalent of throwing gasoline onto a fire.

The biggest change is in the age at first screening, and herein lies the basis for the controversy. In order to save one woman in her 40s from death from breast cancer, 838 women would have to undergo annual screening for 6 years. This amount of screening would result in hundreds of biopsies and many low-aggression cancers being treated as if they were more aggressive than they really are.⁴ This represents a significant downside to the screening process and also makes it costly. However, it is not without

benefit, as breast cancer strikes many women early in life and is the cancer that is associated with the most years of life lost. Many women, if faced with the risks of increased anxiety and possibly unnecessary biopsies and over-treatment, would be prepared to face these negative, costly disadvantages to avoid dying of breast cancer.

The way to improve the situation is not necessarily more mammography but, perhaps, better methods of risk evaluation. The USPSTF guidelines represent an accurate interpretation of the state of the art in mammographic detection of breast cancer. In the best of all possible worlds, doctors and their patients would be able to sort through personal preferences and background risk and come up with an acceptable screening plan for each patient under age 50. However, it is likely that third-party payers will interpret these guidelines as prohibitive of mammography prior to age 50, and many may choose not to pay for them. This will then leave the patient responsible for both the decision and the cost of the screening test. Sadly, then, the apparent "choice" in this situation will only accrue to women who can afford to pay out of pocket for their mammograms. Poor

women will not have a choice.

Regardless of the social fallout and the media buzz generated by the new recommendations, we are still not where we want to be in terms of optimal breast cancer screening. By centering the controversy over the exact timing of mammography screening, we risk behaving like the drunk under the streetlight, looking for the key insight in the wrong place!

Breast cancer biology is a topic of intensive research, and there have been huge breakthroughs in recent years. Scientific insight into estrogen-receptor biology has led to major advances in estrogen-targeted prevention and chemotherapy.¹⁰⁻¹²

In this issue of *Menopausal Medicine*, Drs Ghosh and Vachon provide a comprehensive examination of the importance of breast density as a dominant risk factor for the development of breast cancer, highlighting the role that genetics and hormones play in maintaining breast density in postmenopausal women. Increased breast density has emerged as a dominant, detectable, and modifiable risk factor for the subsequent development of breast cancer in women. In many ways, this issue's authors

FROM THE EDITOR

TABLE US Preventive Services Task Force guidelines for breast cancer screening

2009 RECOMMENDATION	2002 RECOMMENDATION	CHANGE
Against mammographic screening prior to age 50	Against mammographic screening prior to age 40	10 years' delay in first screening mammogram
Biennial screening mammograms beginning at age 50	Screening mammograms every 1 to 2 years beginning at age 40	As above
Individualized recommendations below age 50	Individualized recommendations below age 40	As above
No clear benefit of mammographic screening after age 75	No specific recommendation	—
No clear benefit of CBE	No clear benefit of CBE	No change
Against BSE	No clear benefit of BSE	Discourages BSE
Insufficient evidence to recommend digital or MRI breast screening	No specific recommendation	—

BSE, breast self-examination; CBE, clinical breast exam.

provide a hopeful and constructive way to address the mammography controversy. It may be that future research can be directed toward the detection of preexisting conditions (such as gene mutations) that put women at risk for highly aggressive cancers. These women can be identified early in life. Additionally, factors that increase a more mature woman's risk of cancer, such as breast density, can be identified in midlife.

Enhanced imaging techniques, such as digital mammography and MRI,¹³ can be deployed effectively in this smaller group of high-risk women to arrive at a more balanced and appropriate ratio of not only cost-effectiveness but also harm to benefit.

It's time to take out the flashlight, move away from the streetlight, and help the drunk make his way back to the car keys he dropped on his way out of the bar (and have a designated

driver take him home, please!) We need to call upon medical science to come up with better ways to identify women at the highest risk for breast cancer and target intensive screening and prevention strategies to these women. We must not rely on mammography to "solve" the problem of early detection of breast cancer. We need to get back to the biology of this disease and outsmart it. We owe it to our patients.

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