COMMENTARY

A Tangled Web: Factors Likely to Affect the Efficacy of Screening Mammography

Cornelia J. Baines, Rachel Dayan

Given the direct and indirect costs of mammographic breast cancer screening in North America *(1,2)*, any evidence leading to the improved efficacy of screening mammography should be welcome. The importance of high technical standards to achieve mammographic accuracy has been recognized *(3)*. Improved accuracy should lead to improved efficacy, namely, further reductions in mortality from breast cancer.

The efficacy of breast screening is most contested in women who are 40–49 years old *(4)*, many of whom are premenopausal. In this group, a 16% reduction in breast cancer mortality has been observed 7–10 years after the initiation of screening *(5)*, about half of that observed in women who are 50–69 years old. Although mammographic sensitivity is indisputably lower (less accurate) in younger women, one expert has asserted *(6)* that "Nothing magical happens at age 50. There is no significant difference in breast tissue as seen by mammography" when women in their 40s are compared with women in their 50s. Tabar et al. *(7)* attributed the smaller benefit of screening women in their 40s to shorter sojourn times in some women and to the long interval between screening examinations that occurred in the Two-County Trial. This commentary will give an overview of available information about biologic and life style factors that may reduce the accuracy of screening mammography and thereby also reduce screening efficacy.

Among the factors diminishing the efficacy of screening (Table 1), false-negative mammograms are of crucial importance. Delay in the detection of breast cancer must reduce the opportunity to reduce mortality. This conviction led to a study of menstruating women that found that the chances of a woman having a false-negative mammographic examination were almost doubled in the luteal phase of the menstrual cycle compared to what the chances were in the follicular phase, although only in women who had ever used exogenous hormones (presumably oral contraceptives) *(8)*. Possible biologic mechanisms that could explain this observation are increased mammographic density associated with breast tissue changes in the luteal phase and luteal mastalgia (pain) restricting mammographic compression.

More recently, White et al. *(9)* reported a small but statistically significant increase in mammographic density in the luteal phase. This observation is consistent with the increase in false-negative mammograms previously reported *(8)*, with the conclusion that early breast cancer detection is more difficult to achieve in younger women *(10)* and with the generally accepted notion that increased density (variously described as mammographic, parenchymal, and fibroglandular) is associated with decreased mammographic sensitivity (Table 2).

Table 1. Factors likely to affect breast cancer screening efficacy

- False-negative mammograms
- Interval between screening examinations
- Skilled clinical breast examination at time of mammography
- Tumor characteristics

To identify other factors that may reduce screening efficacy by reducing mammographic accuracy in both premenopausal and postmenopausal women, it may be useful to consider the following issues:

- What changes occur in the breast during the menstrual cycle?
- What characterizes the postmenopausal breast?
- How do reproductive history, age, body mass, and hormone replacement therapy (HRT) impact on mammographic density?
- What effect does menstrual cycle phase have on mammographic interpretation?
- How does density affect mammographic interpretation?
- What are the implications of this tangled web of physiologic and exogenous phenomena?

Breast Tissue Changes During the Menstrual Cycle

The breast changes that occur during the menstrual cycle include subjective symptoms (heat, swelling, and pain); quantifiable changes in volume and temperature; histologic changes

Table 2. Factors likely to affect mammographic accuracy

Endogenous factors affecting density
- Age at time of screening
- Age at first birth
- Parity
- Phase of menstrual cycle
- Menopausal status
- Body mass index
- Height

Exogenous factors affecting density
- Diet
- Oral contraceptives
- Hormone replacement therapy

Technical factors
- Technically excellent mammography
- Interpretive skills of radiologist

Affiliations of authors: C. J. Baines (Department Public Health Sciences), R. Dayan (Department of Pediatrics), University of Toronto, Canada.

Corresponding author: Cornelia J. Baines, M.D., 12 Queen's Park Cres. W., Toronto, ON M5S 1A8, Canada (e-mail: cornelia.baines@utoronto.ca).

See "Note" following "References."

including involution, proliferation, and apoptosis; changes in water content; and changes in magnetic resonance imaging characteristics.

Physical Changes

Subjectively, women report increased nodularity and a sense of fullness *(11)* and changes in breast temperature and tenderness *(12)* during the menstrual cycle. In women who reported breast swelling and cyclic mastalgia, Deschamps et al. *(13)* observed a threefold increase in risk of having mammary dysplasia that involved 50% or more of breast parenchyma.

Objectively, volume changes and temperature changes have been detected. With the use of water displacement to measure changes in volume, Milligan et al. *(14)* found that breast volume was maximum in nulliparous women on day 25 of the cycle. The mean total change in volume was 100 mL for natural cycles and 66 mL for women using oral contraceptives. Simpson et al. *(15)* reported a cyclical increase in the surface temperature of the breast that peaked during the luteal phase.

Histologic Changes

Microscopic changes include involution during the follicular phase and proliferation during the luteal phase with mitosis, lobule size, and the number of acini, all reaching a maximum during the latter half of the luteal phase *(16).* Potten et al. *(17)* observed that, in menstruating women, breast epithelial proliferation peaked at day 21 and was negatively associated with age. Apoptosis is maximal in the late luteal phase *(18).* Malberger et al. *(11),* using preovulatory and postovulatory fine-needle aspirates of breast tissue, reported that nuclear features of the cells collected in the luteal phase (larger, less compact, and with a more prominent nucleolus) enabled investigators to identify all of the aspirates as preovulatory or postovulatory, when aspirates from the same woman were compared. More recently, Olsson et al. *(19),* examining normal breast epithelium from 58 women undergoing reduction mammoplasties, found that this tissue had a statistically significantly higher proliferative rate in the luteal phase than in the follicular phase. Soderqvist et al. *(20)* used the proliferation marker Ki-67/MIB-1 monoclonal antibody in biopsy specimens from 25 women who underwent fine-needle biopsy twice in the same menstrual cycle. The median percentage of MIB-1-positive cells doubled in the luteal phase compared with the value observed in the follicular phase. Gompel et al. *(21)* observed that expression of tyrosine transmembrane receptors, such as epidermal growth factor and c-erbB-2, which mediate proliferation, is higher in the luteal phase than in the follicular phase. Dabrosin et al. *(22)* has shown that ornithine, an amino acid required for cellular growth and differentiation, decreases late in the menstrual cycle, coinciding with the luteal peak in proliferation and apoptosis.

Even though it is well established that proliferative activity is maximal in the luteal phase, it cannot sufficiently explain the 20% increase in breast volume. Glandular tissue accounts for only 10% of the volume of a breast. Other changes that occur are water retention and increased vascularity *(18,23).* Anderson *(18)* suggested that hormonal fluctuations may increase acid mucopolysaccharides in the breast ground substance, thereby increasing the water content of breast tissue.

Changes Detected by Magnetic Resonance Imaging

In 1990 Fowler et al. *(24)* used magnetic resonance imaging to evaluate menstrual cycle-related changes in the breast. They found that breast volume, water content, and the T1 relaxation time were lowest on days 6–15, began to rise on day 15, and peaked on day 25. Between days 16 and 28, parenchymal volume, T1 relaxation time, and water content increased by 39%, 15%, and 24%, respectively. Five days after menses onset, parenchymal volume fell by 30% and water content fell by 17%. Changes of smaller magnitude were reported by Graham et al. *(25)* who used a 1.5-tesla magnetic resonance imager on seven subjects twice a week over at least one menstrual cycle. They concluded that "variations in breast tissue during the cycle are detectable . . . . The variation in breast water content and fibroglandular volume correlates qualitatively with the known effects of hormones on breast structures." However, Graham et al. *(25)* found the variations to be sufficiently small that they are "unlikely to impact on clinical assessment of unenhanced magnetic resonance breast images." Kuhl et al. *(26)* recommended that magnetic resonance imaging should be done within the second week of the menstrual cycle (days 7–13) because during this phase there will be statistically significantly fewer diagnostic problems. Muller-Schimpfle et al. *(27)* concluded that, during days 7–20 of the menstrual cycle, there was a statistically significantly lower parenchymal enhancement with magnetic resonance imaging than from day 21 to day 6. Thus, "confidence in excluding or detecting constant 'real' lesions" might be increased from day 7 through day 20.

Features of the Postmenopausal Breast

Breasts of postmenopausal women have less epithelial tissue and more fatty tissue and are radiologically less dense than breasts of younger women.

Anastassiades et al. *(28)* evaluated breast composition in 112 mastectomy specimens from women at different ages and found that, at ages 31–40 years, 54% of breasts were classified as predominantly "solid tissue" (mammary parenchyma and fibrous stroma) and none of the breasts were extremely fatty. In specimens from women older than 70 years, 46% were fatty and only 8% had solid tissue. Brisson et al. *(29),* who analyzed data from 55 000 women in the Breast Cancer Detection Demonstration Project, reported that menopause was associated with decreased mammographic density. For example, 23% of premenopausal women aged 50–54 years had fatty breasts compared with 30% of postmenopausal women the same age. Spicer et al. *(30)* believe this is because menopause is associated with reduced mitotic activity in breast epithelial cells. Boyd et al. *(31)* observed a 9% reduction in percent density in women who became menopausal in the period of observation. Percent density was the proportion of radiologically dense breast expressed as a percentage of the entire projected area of the breast.

Factors Affecting Mammographic Density

It is generally accepted that increased mammographic density reduces mammographic accuracy. To increase understanding of the many variables that potentially reduce screening efficacy, factors are briefly reviewed that are known to affect density, such as menstrual cycle, reproductive history, body build, diet, and hormone use.

Menstrual Cycle

One study to date has shown an association between phase of menstrual cycle and mammographic density. Density was increased in the luteal phase *(9).*

Reproductive History, Age, and Body Build

As long ago as 1987, Bergkvist et al. *(32)* concluded that reproductive history has a lifelong impact on mammographic parenchymal patterns. Univariate analysis showed increased density with increasing age at first birth, but density was highest in nulliparous women. Brisson et al. *(29)* observed that the percentage of women with mammographic densities (breasts described as “glandular” or homogeneously dense in contrast to atrophic, fatty, or “intermediate”) decreased as age, body weight, and parity increased; however, the percentage with densities increased with increasing height. White et al. *(9)* reported an inverse relationship between body mass index and mammographic breast density. Laya et al. *(33)* concluded that density is directly related to height and inversely related to parity and weight.

de Stavola et al. *(34)* in a multivariate analysis showed that the odds for high-risk Wolfe grades (i.e., density) were statistically significantly lower with increasing Quetelet’s index (i.e., body mass index) and with increasing parity in premenopausal and postmenopausal women. They observed that density increased with age until menopause, where it peaked, and then declined in the absence of HRT. This was also observed by Bergkvist et al. *(32)*. Recently, Kolb et al. *(35)* have shown a very clear relationship between increasing age and decreasing mammographic density in 11 220 patients: densities involving more than 50% of breast volume decreased from a prevalence of more than 60% in women who were 30–39 years old, to slightly more than 20% in women who were 50–59 years old, and to about 10% in women who were 80–89 years old.

A broad picture emerges suggesting that mammographic density is increased in association with nulliparity, increased age at first birth, increasing height, and HRT use. In contrast, mammographic density is decreased with increasing parity, increasing body mass index, and increasing age.

Diet

It has long been suspected that the high fat intake that characterizes the North American diet at least partly explains the higher breast cancer incidence rates relative to other parts of the world. Because “extensive dense breast tissue seen on mammography is associated with an increased risk of breast cancer,” Boyd et al. *(31)* recruited women who had radiologic densities in more than 50% of their breast tissue and randomly assigned them to a low-fat diet (fat = 21% of calories) or to a control group (fat = 32% of calories). Two years later, they did follow-up mammography with 817 women. They observed that the area of dense tissue (expressed in square millimeters) was influenced most strongly by menopausal status with a lesser effect from weight change. In addition, the reduced-fat diet also had a statistically significant effect: after controlling for weight loss, menopausal status, and age at entry, the intervention group (on a reduced-fat diet) showed a statistically significant ($P = .03$) 6.1% reduction in the area of density compared with a 2.1% reduction in the control group.

Although the effect reported is not large, it was one that occurred over a 2-year period and might well increase in magnitude if the intervention continued. It suggests one strategy that might reduce mammographic density. The consequences could be improved mammography and reduced risk of breast cancer. The fact that increased body mass index is associated with a decrease in density appears inconsistent. However, the explanation for the inconsistency may lie in the relative contributions of carbohydrate, fat, and protein to total caloric intake and the as yet undetermined interaction between estrogen and dietary components.

Hormone Replacement Therapy

Although HRT is generally accepted as being directly associated with mammographic density, a summary of current information can be confusing because this issue has been approached in diverse ways. Some studies have compared women using HRT to women who do not use HRT (nonusers); others have done before-after comparisons (before and after onset of HRT); and still others have done before-after studies comparing women initiating HRT with women not using HRT. HRT, the agent of interest, is variably defined with some studies including very detailed data on drug formulation and others not.

And finally, the outcome measure, mammographic density, can be subjectively and qualitatively rated as with the Wolfe classification *(36)* or objectively and quantitatively rated with actual measurement of density as a percentage of total breast area *(37)*. Not all studies have evaluated intraobserver and interobserver agreement.

Based on qualitative analyses and a comparison of nonspecified HRT users with women who did not use HRT, a higher prevalence of mammographic densities has been shown with hormone use *(34,35,38)*.

Other studies have compared mammograms before and after initiation of hormone therapy. In a series of 30 women, HRT was associated with qualitatively increased density in five women (17%), all on combined HRT. Increased density was not observed in the 14 women receiving estrogen alone *(39)*. Stomper et al. *(40)* also reported qualitative increases in density after the onset of HRT that occurred in 24% of the women. The difference observed when comparing women on combined HRT versus women on estrogen alone was not statistically significant, although increased density was more prevalent in the former group.

Another before-after study included 33 postmenopausal women on HRT and a comparison group of 31 nonusers. Over time, there was a subjective increase in density in nine women (27%) using hormones with no differences noted by type of therapy *(41)*. In contrast, a study of 41 women before and after initiation of combined HRT showed that a qualitative increase in density occurred in 24% and a quantitative increase occurred in 73%. However, the quantified increase was visually detectable in only 32% of women *(33)*. These authors speculated that progesterone may cause “greater mammographic changes” than estrogen, which is consistent with the observations of Baines et al. *(8)* and White et al. *(9)*.

Further confirmation of this concept is found in a Dutch study *(42)* of 81 women. This study reported a qualitative increase in density in 8.7% of women on estrogen alone compared with 31% of women on combination HRT. Additional support comes from a Swedish study *(43)* of more than 1000 women that found that 28% of women on combined HRT had an increase in qualitative density compared with 5% of women on estrogen alone and 3% of nonusers.

It is biologically plausible that HRT would increase mammographic density. Such an association has been observed repeatedly and is consistent with the belief that the decreased density seen in postmenopausal women is related to cessation of ovarian hormone secretion. Whether increased density is mainly a progesterone effect needs to be further investigated.

Factors Affecting Mammographic Accuracy

Menstrual Cycle Phase

Baines et al. *(8)* reported an increased risk of false-negative mammograms from women in the luteal phase of the menstrual cycle (sensitivity and specificity of 48.9% and 96.5%, respectively) compared with those from women in the follicular phase (sensitivity and specificity of 59.5% and 96.2%, respectively). The increased risk was observed only in women who had ever used hormones. The luteal decrease in sensitivity is consistent with the observations of Fowler et al. *(24)* and Graham et al. *(25)*. These studies reported that water content increased in the luteal phase. The luteal decrease is also consistent with the observations of Graham et al. *(44)* who reported that relative water content, as determined by magnetic resonance imaging, showed a strong positive correlation with percent density, as determined by digitized x-ray mammograms. Further support for these findings comes from White et al. *(9)*, who, after evaluating mammograms from 2500 menstruating women, concluded that there was a small (4%) but statistically significant increase in density in the luteal phase.

Mammographic Density

Given that increased mammographic density has been reported to be associated with reduced mammographic sensitivity, which leads to a corresponding increase in false-negative mammograms *(45–47)*, investigators have examined the effect of factors associated with increased density, such as HRT and menopausal status, on the sensitivity of mammography. Laya et al. *(48)* studied 8779 postmenopausal women who were more than 50 years old and found that the current use of estrogen replacement therapy was associated with lower specificity and sensitivity of screening mammography when current users were compared with past and never users. The unadjusted mammographic sensitivities with 95% confidence intervals (CIs) for never users, past users, and current users of estrogen replacement therapy were 94% (95% CI = 80%–99%), 94% (95% CI = 69%–99%), and 69% (95% CI = 38%–91%), respectively. In contrast, specificities were stable at 85%, 85%, and 82%, respectively, with narrow confidence limits. Thurfjell et al. *(49)* studied screening results in more than 11 000 postmenopausal women in Sweden and did not observe a decrease in sensitivity in women currently using HRT. Specificity was 94% in current users compared with 95% in former and never users. These authors concluded their results are compatible with Laya et al. *(48)* because of the wide CIs. However, because very different methodologies were used, it is difficult to compare the two studies.

Kerlikowske et al. *(50)* studied mammographic sensitivity in 28 271 premenopausal and postmenopausal women and found, at a 13-month follow-up, the expected age effect with 93.2% sensitivity in women who were 50 years old or older and 83.6% for women who were younger than 50 years old. This difference was even more pronounced if the comparison was restricted to women with fatty breasts, where sensitivity was 98.4% for older women and 81.8% for younger women. These results raise the question: Why is there an age-specific reduction in sensitivity in the absence of density?

Furthermore, it was only in women older than age 50 years that a density effect on mammographic interpretation was observed. In this age group, higher sensitivity was observed in women with fatty breasts than with dense breasts. A similar phenomenon was not observed in women younger than age 50 years. However, it should be noted that in this study, false-negative mammograms were conservatively estimated because interval cancers (diagnosed between screening examinations) were not deemed to be signals of false-negative mammograms if the interval cancer was nonpalpable. Identification of false-negative mammograms was also impeded by the absence of a routine clinical breast examination at the time of the screening examination, which may be especially important for younger women *(51)*. In addition to the opportunity for an underestimate of actual false-negative screening examinations, the qualitative density rankings were performed by a single radiologist with no report of intraobserver variation or reproducibility, as has been reported in other studies *(33)*. Finally, the intervals used for estimating sensitivity are idiosyncratic at 7, 13, and 25 months.

Nonetheless, the findings of Kerlikowske et al. *(50)* are difficult to reconcile with the proposition that factors that increase density may explain decreased accuracy and, therefore, efficacy of screening mammography in younger women. Given the evidence that has been reviewed, uncertainty remains. Certainly, factors other than density are involved, including variations in mammographic technologic and interpretive skills, too long an interval between screening examinations, and more rapid tumor growth rates in younger women.

Finally, based on the assumption that hormone therapy is linked to increased density and decreased mammographic sensitivity, Harvey et al. *(52)* found that HRT cessation for 10–30 days resulted in resolution of mammographic abnormalities in 35 of 47 patients. They concluded that short-term hormone cessation may improve both sensitivity and specificity of mammography. This conclusion is consistent with the concept that HRT inhibits normal involution in postmenopausal breasts *(38)*. HRT cessation may permit involution to resume.

Conclusion

Clearly there are subjective, histologic, and imaging changes in the breast tissue during the menstrual cycle. There is also evidence to believe

- that the postmenopausal breast involutes and this process of involution may be impeded by HRT;
- that mammographic density appears to be related to age, age at first birth, height, body weight, parity, diet, phase of menstrual cycle, menopausal status, and exogenous and endogenous hormones; and
- that increased mammographic density probably reduces mammographic accuracy and screening efficacy.

Mammography clearly is not equally effective for all women. Its success in detecting breast cancer early is known to be improved by technical and interpretive excellence. What is not known is how important the combined effects and interactions of reproductive history, age, exposure to exogenous hormones, phase of menstrual cycle, and diet are in determining the success of screening. Given the high priority attached to controlling breast cancer in North American society, it is crucial to give attention to all factors that may diminish the benefits of mammography.

Currently, many women are eager to enhance their health and to protect themselves as much as possible from breast cancer. It seems only right to translate current knowledge into something applicable at a societal level without conferring harm. What may individual women decide to do?

- They may choose to restrict their fat intake substantially and in so doing reduce the risk of cardiovascular disease, reduce one risk factor for breast cancer *(31)*, and possibly enhance the accuracy of their mammograms by reducing mammographic density *(31)*.
- Premenopausal women may choose to schedule their mammograms in the follicular phase of their cycle again to enhance mammographic accuracy *(8,9)*.
- Postmenopausal women may choose to discontinue HRT for a brief period before their mammograms to diminish the likelihood of false-positive mammograms *(52)*.
- Some women reject HRT and seek alternative means to control postmenopausal symptoms. One consequence of such a decision would be the avoidance of increased mammographic density, which is observed in about 25% of HRT users *(39–41)*.

What research questions need to be addressed? Do women with cyclic mastalgia, with its association with increased density, constitute a special group less likely to benefit from mammography screening? What are the phenomena at the cellular level that are associated with or explain mammographic parenchymal densities? Is there a connection between oral contraceptive use and an increased risk of false-negative mammograms in the luteal phase of the menstrual cycle? Why does HRT qualitatively increase density in only about 25% of women? In women on combined HRT, should mammograms be timed to avoid the progestin component? What factors are associated with the decrease in mammographic sensitivity in younger women with fatty breasts compared with older women observed by Kerlikowske et al. *(50)*. Perhaps most important of all would be a better understanding of the relative importance of variables such as age, reproductive cycle, diet, body mass, menstrual cycle, and HRT and the nature of their interactions.

Everything possible should be done to identify the optimal biologic conditions for enhancing mammographic efficacy. Even better would be a new imaging technology that would surpass the best that "modern mammography" can achieve. Best of all, would be a blood test that could identify women who were at increased risk of breast cancer or who already had occult breast cancer. The tangled web still needs unraveling.

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NOTE

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