Menstrual Cycle Variation in Mammographic Breast Density: So Who Cares?

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So who cares? Is it really important that there is a 4% excess in the proportion of women with mammographically "extremely dense breasts" in the luteal phase of the menstrual cycle compared with the follicular phase? For that is what White et al. (1) have clearly shown in this issue of the Journal in a study based on an analysis of 2591 menstruating women who had screening mammograms in a health maintenance organization during the last 7 months of 1996.

My opinion is that this excess is important. As White et al. (1) point out, increased mammographic density is associated with decreased mammographic sensitivity and decreased mammographic specificity. Both of these operating characteristics put younger women at a disadvantage compared with older women in terms of benefiting from the early detection of breast cancer. As for the small size of the effect (4% overall), it is often overlooked that a small effect on a large population can have an impact far greater than a large effect on a small population. When millions of women are being encouraged to seek mammographic screening in their forties, even a small effect may prove to be important.

Women in their forties who undergo mammographic screening are facing high probabilities of false-positive screens, namely, a 30% cumulative risk after five mammograms and a 56% cumulative risk after 10 mammograms (2); however, they achieve only a rather small and delayed benefit in terms of a reduction in breast cancer mortality when they are screened in their forties (3,4). Women surely will welcome any opportunity to enhance mammography’s effectiveness. Follicular timing may appeal to them.

White et al. (1) found that body mass index (BMI) had the strongest association with breast density overall. Fifty-three percent of women in the lowest BMI quartile had extremely dense breasts compared with 5% in the upper quartile. However, even after adjustment for BMI, menstrual cycle phase was associated with breast density. When women were stratified by BMI (above and below the median), the association of menstrual phase with density was stronger for women in the lower half (P<.01). The proportions of leaner women with extremely dense breasts in the luteal phase were 46% for week 3 and 45% for week 4, while in the follicular phase, the proportions were 40% for week 1 and 35% for week 2.

White et al. refer to a 1997 Canadian Study (5). That study found that the risk of a false-negative mammographic examination was significantly elevated (unadjusted odds ratio = 2.16; adjusted odds ratio = 1.47; P = .05, two-sided) among women who had mammograms during the luteal phase compared with women who had mammograms during the follicular phase. Mammographic sensitivity in the Canadian study was higher in the follicular phase (60%) than in the luteal phase (49%), but the difference was not statistically significant. The Canadian study was disadvantaged in two respects. First, the mammograms were collected over a prolonged period, 1980–1987. Second, the women reported only the day on which their last period began but not their usual cycle length. In contrast, White et al. examined mammograms from a 7-month period in 1996. Furthermore, White et al. knew the usual length of each woman’s cycle, allowing a more accurate categorization of the follicular and luteal phases. Another point of difference between the study by White et al. and the Canadian study is that, in the Canadian study, women received annual screening, contributing 32,000 mammograms for analysis of menstrual phase impact on outcomes.

After they published their results, the Canadian researchers were repeatedly asked: Why were false-negatives more likely in the luteal phase? Because the research purpose had been to identify the influence of menstrual phase on operating characteristics and not to explain the underlying biologic mechanism or to evaluate radiologic images, their answers were speculative, based on what is known, for example, about cyclic changes in breast tissue and changes in mammographic density associated with hormone replacement therapy.

White et al. have begun the process of providing evidence-based answers to the question "Why?" We knew that breast density decreases mammographic sensitivity, and now we know that breast density is higher in the luteal phase, which may explain (if only partially) the increased risk of false-negative mammograms in the luteal phase. It is exciting to see two complementary reports within less than a year, one demonstrating that operating characteristics are improved in the follicular phase (5) and the other demonstrating that an objectively measurable imaging feature is consistent with these operating characteristics (1). Still to be unraveled is the perplexing role of previous oral contraceptive use, because it was only in women...
with such a history that the luteal false-negative phenomenon was observed in the Canadian study. Are menstruating women who have never used oral contraceptives at an advantage for mammographic imaging? And if so, why? Furthermore, we still have no measure of within-woman cyclic changes. All that is needed is an observational study in which premenopausal volunteers would agree to have split mammographic screening in the same menstrual cycle: one breast imaged in the follicular phase and the other in the luteal phase, with the technique kept as constant as possible.

But an even more important question has been waiting to be answered ever since Tabar et al. (6) published their first results from the Two-County Study in Sweden back in 1985 that showed excess breast cancer mortality in screened women aged 40–49 years. This mortality paradox is clearly displayed in a recent updated overview of the Swedish randomized trials (7) and parallels similar observations in the 7-year results from the Canadian National Breast Screening Study (8). However, as the end of the 1990s approaches, we know that the mortality paradox extinguishes itself 7 or more years after screening is initiated. So now the question is not so much: Why was the paradox ever observed? It is rather: Why is the benefit from screening this age group so small relative to screening older women, and why is the benefit so delayed? Even today, after many years of follow-up, two of the Swedish studies (7), Ostergotland (part of the Two-County Study) and Stockholm, show equal breast cancer mortality in screened and unscreened groups aged 40–49 years.

Can we agree that the arbitrary cutoff, age 40–49 years versus 50–59 years, used in the analysis of screening trials is a crude proxy for a cutoff that separates mainly premenopausal women from mainly postmenopausal women? If so, we should be seriously asking ourselves: Do the menstrual cycle and related endogenous hormones hold the secret of why younger women do not benefit more from screening and subsequent therapy? There is much more to be found out. Quickly please.

References


Serum Insulin-Like Growth Factor-I Levels and Prostate Cancer Risk—Interpreting the Evidence

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For men, cancer of the prostate is the most frequently diagnosed cancer and benign prostatic hyperplasia is the most common benign disease. One in every four men in the United States will require surgery for either prostate cancer or benign prostatic hyperplasia by the time they reach age 80, amounting to nearly half a million surgeries with medical costs of more than 5 billion dollars per year (1). A heightened awareness of the scope of the problem that prostate cancer represents has resulted in the widespread use of prostate-specific antigen (PSA) testing, an extremely sensitive (but not entirely specific) method for diagnosing the disease (2,3). The etiology of prostate cancer is currently unknown, but the involvement of growth factor abnormalities in this disease has long been suspected (4).

Specifically, insulin-like growth factor (IGF) has been implicated in prostate cell proliferation (5). The IGFs, IGF-I (also known as IGF-1) and IGF-II, are tightly bound (both in the circulation and in tissues) to a family of six proteins known as the IGF-binding proteins (IGFBPs), of which IGFBP-3 is the most prevalent in serum (6). Levels of serum IGF-I and serum IGFBP-3 are co-regulated by growth hormone (GH), as well as by nutritional and genetic factors (7). The genetic regulation of IGF-I levels in tissue and in serum has familial and ethnic components, which also appear to affect height achieved during development and determine the risk of osteoporosis in adults (8). In vitro studies of benign and malignant prostate tissues and cell lines demonstrated that IGFs, IGF receptors, and IGFBPs are

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876 EDITORIALS

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