Biological Significance of Interventions That Change Breast Density

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Mammography provides an image, albeit imperfect, of what is inside the breast. Women with high levels of mammographic density, which reflects the relative proportion of glandular and stromal tissues to fatty tissue in the breast, have been consistently shown in observational studies to have a high risk of developing breast cancer (1–3). In this issue of the Journal, Greendale and colleagues (4) report the effect of 12 months of postmenopausal hormone therapy on mammographic density among women enrolled in the randomized clinical Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial, which tested the effects of several regimens of estrogen plus progestin, estrogen alone as conjugated equine estrogens, and placebo.

The current report builds upon a previous observation in the same PEPI study population (5) by using a computer-assisted technique to provide a continuous measure of the proportion of the breast area that is comprised of dense tissue. The authors’ comparison to a categorical evaluation of density using the four-level Breast Imaging Reporting and Data System (BI-RADS) density grades (6) is informative, and highlights the need for standardized measurement criteria in this area of research. However, in the current report, it is not clear why the authors provide an adjusted analysis rather than an intent-to-treat comparison between the intervention arms and placebo arm of the study. This decision suggests that there may have been imbalance between the study arms with respect to mammographic density at study baseline. In any event, the authors observed a statistically significant increase in breast density among women who received the estrogen plus progestin combinations but not for those who received estrogen alone, which is consistent with prior reports (5,7–10), at least for continuous combinations of these hormones (11). The effects of the hormone preparations, however, were relatively small in that there was a less than 5% absolute mean change in the proportion of breast area made up of dense tissue. The authors themselves raise the most critical question—what is the link between such changes in breast density in women receiving postmenopausal hormone therapy and subsequent changes in breast cancer risk?

Recently, a substantial genetic component has been associated with the underlying differences in breast density among women (12). In addition, high mammographic density in greater than 75% of the breast area has been associated with an increased incidence of proliferative histologies and/or noninvasive cancers in the breast (13). Such observations perhaps explain much of the relationship between substantial, long-standing high breast density and breast cancer risk, but they leave a different question unanswered: Does a relatively short-term, modest change in breast density that is associated with an intervention carry the same breast cancer risk implications as does underlying differences in breast density? Moreover, does breast density change represent a modifiable risk factor that might be useful in identifying intervention strategies?

The available literature on intervention studies with breast density endpoints can be viewed as making a series of predictions; many of these predictions are currently under evaluation in full-scale randomized clinical trials of breast cancer risk reduction. These predictions and the status of potentially confirmatory trials are outlined below according to the type of intervention tested. Estrogen plus progestin has been shown to increase breast density, whereas estrogen alone has had a limited or no measurable effect on this endpoint (5,7,8). Tamoxifen has fairly consistently decreased breast density (14–17), whereas the effects of raloxifene on breast density have been mixed (18,19). Finally, dietary fat intake reduction also reduced breast density in a prospective trial (20).

Information will be available soon from randomized clinical trials that are designed to determine the effects of such interventions on breast cancer outcome. Indirectly, these trials will provide information on the value of short-term changes in breast density in predicting an intervention effect on breast cancer risk. One such trial, within the Women’s Health Initiative (WHI) with 16,608 postmenopausal women participants, has reported an increase in the number of breast cancers after approximately 5 years of combined conjugated equine estrogens plus medroxyprogesterone acetate use (21). Another WHI randomized trial that is evaluating estrogen alone for women with prior hysterectomy continues with active Data Safety Monitoring Board oversight of 10,739 randomized women. The National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 trial (22) and several European trials (23–25) have followed more than 27,000 women who were randomly assigned to receive tamoxifen or placebo for primary breast cancer risk reduction. Taken together, the results of these trials demonstrate an overwhelming proof of principle regarding a favorable tamoxifen effect on breast cancer risk, albeit with a clinical utility that is limited by endometrial and vascular side effects (26). The Raloxifene for Use in The Heart (RUTH) trial has randomly assigned 10,211 women who are at a high risk of heart disease to raloxifene or placebo, includes a baseline assessment of breast cancer risk, and has added breast cancer risk as an additional primary endpoint (27). The NSABP P-2 trial, which is comparing raloxifene with tamoxifen, is in the process of successfully completing accrual as scheduled and currently has more than 14,000 participants (28). Dietary fat intake reduction is undergoing randomized clinical trial testing in a population of more than 48,000 postmenopausal women in the WHI Dietary Modification trial for primary prevention of breast cancer (29). In addition, accrual has been completed for two randomized secondary prevention (ad-
juvenile) trials of dietary change, with over 5000 breast cancer patients participating (30–32).

In the WHI, an ancillary study is evaluating relationships among breast density change, study arm, and clinical outcome. Similar or more concerted efforts incorporating breast density change in other ongoing randomized clinical trials targeting breast cancer risk could help to directly evaluate breast density as a modifiable risk factor for breast cancer. It will be of equal importance to test interventions to reduce mammographic density in premenopausal women (33), a group that has a high prevalence of increased mammographic density.

In summary, mammographic density is a useful marker of increased risk for breast cancer and of decreased sensitivity of mammographic diagnoses, and may be a valid marker of the effect of interventions that increase or decrease breast cancer risk. Only time, and ongoing randomized trials, will tell.

REFERENCES


NOTE

Editor's note: R. Chlebowski is a consultant for Astra-Zeneca (Wilmington, DE), the manufacturer of tamoxifen, and A. McTiernan is a principal investigator of a pharmaceutical company (Besins International U.S., Inc.)-sponsored clinical trial of the effects of a tamoxifen derivative on mammographic density.