Tamoxifen, Mammographic Density, and Breast Cancer Prevention

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The ability to predict the future occurrence of disease in individuals allows the improved design and application of preventive strategies and intervention trials and improved clinical decision making (1). Cardiovascular medicine provides a paradigm for an approach to disease prevention based on risk prediction: modification of risk factors has been estimated to account for approximately half of the 40% reduction in age-specific mortality from cardiovascular disease observed over the past three decades, whereas the remainder of the reduction has been attributed to improvements in treatment (2).

Predicting the risk of breast cancer is less well developed than predicting the risk of cardiovascular disease (1). The most widely used current method of predicting risk of breast cancer is the Gail model (3), which includes age, age at menarche, age at birth of first child, number of previous benign breast biopsies, and number of first-degree relatives with breast cancer.

Variations in breast tissue composition, as shown by differences in the percentage of the mammogram occupied by radiologically dense tissue, are associated with four- to fivefold differences in the risk of breast cancer and are more strongly associated with breast cancer risk than the other variables in the Gail model (4,5). Unlike most other risk factors for breast cancer, mammographic density can be changed, suggesting that it may be a target for preventive interventions. The article by Cuzick et al. (6) in this issue of the Journal shows that change in mammographic density induced by tamoxifen may be associated with change in breast cancer risk.

Cuzick et al. (6) conducted a nested case-control study within the first International Breast Cancer Intervention Study, a randomized prevention trial of tamoxifen vs placebo. Case subjects were 123 women diagnosed with breast cancer 12–18 months after trial entry, and control subjects were 942 women without breast cancer. Percent mammographic breast density (PMD) at baseline and after 12–18 months was assessed visually by one reader in 5% increments. Compared with all women in the placebo group, those in the tamoxifen group who experienced a 10% or greater reduction in breast density had a 63% reduction in the risk of breast cancer, whereas those who took tamoxifen but experienced a reduction in PMD of less than 10% had no risk reduction. In the placebo arm, breast cancer risk was similar in subjects who experienced less than a 10% reduction in PMD and those who experienced a greater reduction. The authors conclude that the change in PMD 12–18 months after starting treatment is an excellent predictor of response to tamoxifen in the preventive setting.

Limitations of the study recognized by the authors include the small number of cancers, the small proportion (55%) of mammograms available for eligible subjects, knowledge of case and control status when mammograms were classified (although treatment arm was not known), and the failure to confirm the radiologists’ assessment of images when computer-assisted measurement of digitized images was attempted, apparently because of the poor quality of the digitized images. Furthermore, because only a global assessment of PMD was made, we have no information about whether a decrease in the dense area (which reflects fibro glandular tissue), an increase in the nondense area (which reflects fat), or both were responsible for the change in PMD.

All current methods of assessing PMD, although reliable, are subject to measurement error because they are subjective and assess only an image of the projected area of the compressed breast rather than the volume of breast tissue (7). Measurement error may lead to underestimates of the association between breast density and the risk of breast cancer and the effects of interventions on that association, such as those reported by Cuzick et al. (6). The reduction of PMD by tamoxifen may also make some breast cancers that were previously masked by density detectable and lead to further underestimation of the effect on breast cancer risk reduction (8).

Although it may be tempting to ascribe the effects of tamoxifen, a selective estrogen response modifier, on breast density to the anti-estrogen properties of the drug in the breast, the association between PMD and exposure to estrogen is far from established. For example, most studies of blood levels of ovarian hormones have found either no association or an inverse association with PMD [reviewed in (9)]. Combined hormone therapy, but not estrogen alone, is associated with an increase in both PMD (10–12) and the risk of breast cancer (13). PMD and serum estradiol levels in postmenopausal women are both associated with an increased risk of breast cancer; however, their influences on risk appear to be independent (14). Furthermore, tamoxifen reduces the risk of only estrogen receptor–positive breast cancer, whereas PMD is associated with an increased risk of both estrogen receptor–positive and estrogen receptor–negative breast cancer (15). However, little is known about tissue levels of estrogen in relation to PMD. Other mechanisms that include, for example, insulin-like growth factor 1 (IGF-1), may be involved. Serum and tissue levels of IGF-1 have been associated with PMD (9), and tamoxifen has been shown to reduce serum levels of IGF-1 (16).

Do the results of the study by Cuzick et al. mean that PMD can now be used as a surrogate for breast cancer to examine other approaches to breast cancer prevention? Clinical trials of potential strategies for breast cancer prevention could be smaller, shorter,
and less expensive if change in PMD rather than the development of breast cancer was the outcome.

To be used as a surrogate for breast cancer, PMD should meet the criteria proposed by Prentice (17) and further discussed by Schatzkin and Gail (18). With regard to PMD and tamoxifen, these criteria are as follows: 1) PMD should be associated with risk of breast cancer, 2) PMD should be changed by the intervention (tamoxifen), and 3) the change in PMD should mediate the effect of the intervention (tamoxifen) on breast cancer risk. This means that tamoxifen and breast cancer risk will be unrelated once change in PMD is taken into account. Although the first two of these criteria are met in the article by Cuzick et al., an association between change in PMD and breast cancer risk is shown, no analysis of mediation of the effect is described.

However, even if it was convincingly shown that change in PMD does mediate the effects of tamoxifen on breast cancer risk, it should not be concluded that all other causes of a reduction in PMD would reduce the risk of breast cancer. Obvious counterexamples are age and weight. Average PMD decreases with increasing age (19), whereas breast cancer incidence increases with age. Cumulative exposure to PMD may be the measure that is relevant to breast cancer risk (20). PMD is also inversely associated with body weight (21,22), which is associated with an increased risk of breast cancer in postmenopausal women (23–25). A randomized controlled trial of physical activity for 1 year, which may reduce breast cancer risk (26) in postmenopausal women, showed that some markers of relevance to risk, including serum estradiol, were reduced by the intervention, whereas the nondense area of the breast was decreased and PMD was increased as a result of the weight loss associated with the intervention (27).

The article by Cuzick et al. is an important first step in the evaluation of PMD as a surrogate marker for breast cancer, and the findings should stimulate further research. The most pressing need is for the development of methods for measuring breast density that are objective, automated, quantitative, and volumetric (7). In addition, correlation of the effects of tamoxifen on PMD with its effects on the histology, proliferative state, stroma, and other features of breast tissue would be desirable. It is also important to know whether variations in the response of PMD to tamoxifen are associated with variations in the frequency or severity of side effects of the drug. Other datasets may exist in which these questions could be addressed.

References


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