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Mammographic Density as a Biosensor of Tamoxifen Effectiveness in Adjuvant Endocrine Treatment of Breast Cancer: Opportunities and Implications

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Tamoxifen is highly effective in treating estrogen receptor (ER)–positive breast cancer. Meta-analyses of adjuvant tamoxifen treatment for 5 years have shown reduced breast cancer recurrence at 10 years, with reduced breast cancer mortality observed at 15 years (event rate ratio, 0.70; 95% CI, 0.64 to 0.75).[1] Given that tamoxifen metabolites bind to the ER more avidly than the parent drug, tamoxifen recipients are hypothesized to be divisible into a group of excellent metabolizers, who receive benefit with standard dosing, and poor metabolizers, who do not benefit.[2] Accordingly, the development of validated measures for monitoring tamoxifen effectiveness would have great value, particularly among premenopausal women, a group in which tamoxifen is first-line therapy. We highlight the potential relevance of assessing mammographic breast density as a marker of tamoxifen efficacy, particularly among premenopausal women in a clinical setting.

Mammographic density is a radiologic measure of the fibroglandular content within the breast and is usually expressed as the percentage of total breast area composed of dense tissue.[3,4] Women with the highest levels of percent density (ie, > 75%) experience a four- to six-fold increased relative risk of developing breast cancer compared with women who have the lowest percentage mammographic density when adjusted for confounders.[3,4] Amassing data suggest that a decline in mammographic density could serve as a much-needed predictor of a favorable response to the selective ER modulator tamoxifen.

The results of four retrospective analyses, which include one that evaluated breast cancer–specific mortality among patients with ER-positive disease treated with tamoxifen, indicated that women whose mammographic density declined in the unaffected breast after initiation of tamoxifen therapy had better outcomes (reduced risk of recurrence[5,6] or death from breast cancer[7,8]). The magnitude of the observed benefit associated with a decline (approximately 10%) in breast density was remarkably similar across studies, despite differences in the methods of mammographic density assessment and analytic approaches, which suggests that these findings are robust. The results from studies that included premenopausal women are shown in Table 1. Of the two prior studies that examined tamoxifen-related changes and breast cancer death,[7,8] one excluded premenopausal women,[7] for whom tamoxifen remains as the primary endocrine therapy. Assessment of mammographic density change after tamoxifen treatment, specifically among younger women, merits further study to maximize the potential translational benefit of monitoring mammographic breast density change as a prognostic indicator in the clinic.

In our prior retrospective analysis of patients with ER-positive breast cancer (age range, 32 to 87 years) who were diagnosed at Kaiser Permanente Northwest,[8] we compared the change in mammographic density after 1 year of tamoxifen treatment among 97 patients who died of breast cancer with 252 matched patients who did not. Women who were in the highest tertile of mammographic density decline were less likely to die of breast cancer (odds ratio [OR], 0.44; 95% CI, 0.22 to 0.88).[8] To explore the potential utility of assessing mammographic density decline as a measure of effectiveness among premenopausal women who received adjuvant tamoxifen, we performed a subset analysis that examined recurrences and deaths among 136 women with ER-positive breast cancer diagnosed at age 55 years or younger (a surrogate for premenopausal status) who were included in the initial report. Among these women, there were 34 recurrences or deaths at 5 years of follow-up and 50 such events during the whole study period (1990 to 2010). Although this analysis is limited by statistical power, multivariate Cox proportional hazards regression models demonstrated that patients with ≥ 10% decline in mammographic density after 1 year of tamoxifen therapy had a nonsignificant improvement in disease-free survival (DFS) at 5-year follow-up (hazard ratio [HR], 0.78; 95% CI, 0.38 to 1.61); mammographic density declined among 12 (35%) women with recurrence or who died. Results at 67 months of follow-up were similar (HR, 0.62; 95% CI, 0.65 to 1.21). Consistent with our findings, prior analyses of premenopausal patients found that tamoxifen-associated density decline was associated with a reduced risk of breast cancer recurrence[5,6] (Table 1). Taken together, these

Table 1. Tamoxifen-Associated Changes in Breast Density in Relation to Breast Cancer Outcomes Among Studies That Included Premenopausal Women: Evidence to Date

Authors (study design)	Population	Breast Cancer Outcome	No. of Events Among Tamoxifen Users	Mammo Type; Density Assessment	Time Between Tamoxifen and FU Mammo	Results		
						Premenopause	Postmenopause	Pre/Postmenopause Combined
Present study (case-control)	USA (N = 136)	Recurrence or death	34 at 5 years FU; 50 overall	Film; quantitative (Cumulus)	Mean, 12 months	HR, 0.78 (95% CI, 0.38 to 1.61) at 5-year FU; HR, 0.62 (95% CI, 0.65 to 1.21) overall*†	NA	NA
Nyante et al, 2015 (case-control)[8]	USA (N = 349)	Death	97	Film; quantitative (Cumulus)	Mean, 12 months	OR, 0.44 (95% CI, 0.13 to 1.53) for ≤ 50 years‡	OR, 0.49 (95% CI, 0.19 to 1.29) for > 50 years‡	OR, 0.44 (95% CI, 0.22 to 0.88)‡
Ko et al, 2013 (patient cohort)[6]	Korea (N = 1,066)	Recurrence§	67	Digital; visual (BI-RADS)	Median, 19 months	HR, 0.37 (95% CI, 0.18 to 0.76)‖	HR, 0.41 (95% CI, 0.52 to 3.20)‖	HR, 0.35 (95% CI, 0.17 to 0.68)‖
Kim et al, 2012 (patient cohort)[5]	Korea (N = 1,065)	Recurrence	Not reported for tamoxifen only	Digital; quantitative (Cumulus)	Mean, 13.1 months	Not reported for tamoxifen only	Not reported for tamoxifen only	HR, 1.52 (95% CI, 0.92 to 2.51)¶
Cuzick et al, 2011 (nested case-control)[12]	United Kingdom and Finland (N = 1,065)	Incidence	51	Film; visual (in 5% increments)	Median, 18 months	OR, 0.27 (95% CI, 0.11 to 0.66)#	OR, 0.53 (95% CI, 0.22 to 1.28)#	OR, 0.37 (95% CI, 0.20 to 0.69)#

NOTE. Adapted from Nyante et al.[8]
Abbreviations: BI-RADS, Breast Imaging and Reporting Data System density scale; ER, estrogen receptor; FU, follow-up; HR, hazard ratio; Mammo, mammography; OR, odds ratio.
*HR for ≥ 10% reduction *v* < 10% reduction (referent).
†Age was used as a proxy for menopausal status.
‡OR for ≥ 8.7% reduction *v* < 0.5% reduction (referent).
§Systemic, locoregional, contralateral.
‖HR for recurrence in patients with < 5% reduction *v* those with ≥ 5% reduction (referent).
¶HR for women who downgraded in a BI-RADS category compared with those who did not (referent).
#OR for ≥ 10% reduction in the tamoxifen arm *v* placebo arm.

findings suggest that evaluating premenopausal women for change in mammographic density after tamoxifen therapy may identify patients with a better prognosis.

The value of monitoring change in mammographic density after initiation of adjuvant tamoxifen treatment has not been evaluated in a phase III clinical trial setting. Treatment of premenopausal patients with ER-positive cancer is problematic because these women tend to have a worse prognosis than their postmenopausal counterparts.[9] Accordingly, identification of early predictors of tamoxifen response would have particular value in this group, perhaps by providing encouragement for responders to continue on adjuvant treatment of 10 years rather than 5 years because continuing tamoxifen for 10 years results in a larger reduction in recurrence and mortality.[10] Additionally, the identification of a predictor of tamoxifen response would be useful in indicating the need to consider alternatives for nonresponders.

An example of a trial where the assessment of mammographic density may have proven informative is the recent randomized controlled phase III clinical trial that included participants from the Suppression of Ovarian Function Trial. In this trial, Francis and colleagues[11] examined whether the addition of ovarian function suppression (OFS) to adjuvant tamoxifen therapy compared with tamoxifen therapy alone improved DFS at 67 months of follow-up among premenopausal patients with ER-positive breast cancer. DFS did not differ significantly between the two arms; DFS at 5 years was 84.7% among women who received tamoxifen compared with 86.6% among women in the tamoxifen plus OFS treatment arm (HR for recurrence, 0.83; 95% CI, 0.66 to 1.04; $P = .10$).[11]

Among women who received prior chemotherapy and remained premenopausal, the addition of OFS to tamoxifen resulted in borderline statistically significant improved survival than tamoxifen alone (DFS for tamoxifen with OFS was 82.5% *v* DFS for tamoxifen alone, 78.0% [HR for recurrence, 0.78; 95% CI, 0.60 to 1.02]).[11] Potential markers of tamoxifen efficacy, such as a decline in mammographic density, genotyping for putative markers related to tamoxifen metabolism to its active metabolites, or direct measurement of drug and drug metabolites, were not analyzed. Thus, similar to most clinical trials investigating tamoxifen, Francis and colleagues showed the average effect of tamoxifen among all patients enrolled in the trial, who likely represent a mixture of tamoxifen responders and nonresponders. Given that 30% to 50% of tamoxifen recipients demonstrate a decline in mammographic density,[5-8,12,13] we suggest that the effect of tamoxifen may have been significantly better among women whose mammographic density declined after treatment.

The ability to detect a decline in mammographic density is limited among women with extremely low baseline density measurements. Given that mammographic density is higher in younger women than in older women, and among patients with breast cancer than those in the general population, the majority would be suitable for assessment of a density reduction after tamoxifen treatment.[14,15] Advances in techniques for measuring breast density and the growing availability of these technologies may facilitate implementation of this approach. However, even visual determination of a decline in mammographic density has been predictive of efficacy among tamoxifen recipients (in the chemopreventive setting).[12] To date, most studies, including the results presented herein, have evaluated change in mammographic density among women treated with tamoxifen by using mammograms obtained approximately 12 to 18 months postdiagnosis.[5-8,12] The development of breast imaging technologies that do not rely on ionizing radiation has enabled studies of serial breast density measurements at shorter intervals. Preliminary findings from a study that used ultrasound tomography[16] suggested that tamoxifen-associated decreases in breast density are detectable as early as 3 months after initiation of treatment.[17] Nonionizing breast imaging modalities may be particularly attractive for use among younger premenopausal women among whom avoidance of radiation exposure is highly desirable.

Understanding the mechanisms that explain the relationship of mammographic density decline after tamoxifen therapy with improved breast cancer outcomes may also have important implications for breast cancer prevention. The International Breast Cancer Intervention Study showed that in women at increased predicted breast cancer risk, a decline in mammographic density after tamoxifen chemopreventive therapy is associated with a reduction in breast cancer development.[12] In the International Breast Cancer Intervention Study, women were randomly assigned to receive 20 mg of tamoxifen or a placebo once daily for 5 years. Among tamoxifen recipients, 46% experienced a decline in mammographic density of at least 10%, as visually estimated. Compared with women who received a placebo, tamoxifen recipients whose density fell by 10% or more had a 63% lower breast cancer incidence, whereas the remaining tamoxifen recipients did not experience any reduction in breast cancer incidence.[12] One possible interpretation of this finding is that mammographic density is a true intermediate endpoint in breast carcinogenesis and that the lowering of density is causally related to reducing risk. Alternatively, because tamoxifen is a prodrug that exerts the majority of its effects through its active metabolites, most notably, 4-hydroxytamoxifen and endoxifen (4-hydroxy-*N*-desmethyl-tamoxifen),[18,19] women who do not efficiently metabolize tamoxifen could fail to show a change in density or a lowering of risk, reflecting concurrent, yet unrelated, biologic mechanisms. In this interpretation, density decline is a marker of reduced risk but not its cause, similar to the most likely explanation for the relationship of density lowering and improved outcomes in the adjuvant setting where effects on metastatic cells are the key effect.

Data related to mammographic density change after initiation of aromatase inhibitors (AIs) are inconclusive. A recent study on mammographic density change reported that 14% of 387 white, postmenopausal women with early-stage breast cancer treated with AIs experienced a $> 5\%$ decline over an average of 10 months, which was not significantly different from mammographic density changes among matched healthy control subjects.[20] The authors noted that the results were consistent with five of nine prior reports and that of four discordant studies, only one included a substantial number of patients and examined the relationship with outcome.[5,20] The latter study, which was conducted in a Korean population with considerably higher baseline mammographic density than US patients, found a suggestive relationship between AI-associated mammographic density reduction and recurrence (HR, 7.11; 95% CI, 0.90 to 56.37; $< 5\%$ *v* $\geq 5\%$ reduction [referent]).[5] Vachon et al[20] concluded that the detection of changes in density among postmenopausal women may be difficult because of the

lower baseline density. Future work is needed to determine the relationship between mammographic density change after treatment with AIs and breast cancer outcome.

From a practical perspective, it is important to consider how assessment of breast density change might be achieved in a clinical setting. Much of the research has been carried out on screen-film mammography using area-based approaches (Table 1), which yield semiquantitative or quantitative and reliable measures but often require either trained experts or specialized software for the density assessment. Clinical assessment of breast density in mammography facilities in the United States is routinely determined by visual assessment by a radiologist with the use of the American College of Radiology's Breast Imaging Reporting and Data System, which provides a four-category estimate.[21] New technologies that provide quantitative and automated volumetric density measurements in full-field digital mammography are being evaluated clinically, including methods that have received Food and Drug Administration approval,[22,23] which may facilitate future studies evaluating density change as a marker of treatment effectiveness.

The findings discussed here may also have important implications for breast cancer research and therapy. First, studies considering dose titration of tamoxifen on the basis of metabolite levels might also consider titration against density change.[24,25] Second, although tamoxifen is reportedly less effective in treating postmenopausal ER-positive breast cancers than AIs,[26] these comparisons do not stratify patients into good and poor tamoxifen metabolizers, which suggests that the effectiveness advantage of AIs may only pertain to poor tamoxifen metabolizers. An increase in treatment options for older women is important given differences in adverse effects among drug classes and variable individual tolerance of related symptoms.[27] Third, the use of a biosensor to monitor tamoxifen effectiveness may encourage compliance among premenopausal women where adherence is often low due to the adverse effects associated with tamoxifen.[28,29] Furthermore, the ability of tamoxifen to lower mammographic density may increase sensitivity of screening among some women, which might offer clinical benefits.

In conclusion, the present findings support the importance of collecting breast images pre- and post-tamoxifen initiation and to assess breast density change in future clinical studies to evaluate the effectiveness of tamoxifen or its metabolic derivatives in preventive or adjuvant settings.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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