

EDITORIAL

The Potential for Mammographic Breast Density Change as a Biosensor of Adjuvant Tamoxifen Therapy Adherence and Response

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Within this issue of the *Journal*, Eriksson and colleagues (1) describe the relation of adjuvant therapy with mammographic breast density (MBD) changes among women with breast cancer. Prior studies have demonstrated that tamoxifen-associated MBD decline translates into reduced breast cancer risk in the chemopreventive setting and improved breast cancer outcomes, including reduced risk of recurrence and breast cancer-specific death, in the adjuvant setting (2,3). Previously, this group observed improved prognosis upon MBD decline in the unaffected breast following tamoxifen therapy among breast cancer cases in Sweden (4). This current study builds upon those findings by examining influences of tamoxifen adherence as well as other adjuvant therapy types on MBD decline within 3 years postdiagnosis in a prospective cohort of 2490 Swedish breast cancer patients diagnosed between 2001 and 2015. They show that patients who received adjuvant tamoxifen were more likely than patients not prescribed endocrine therapy to experience MBD decline, consistent with prior reports (2,3). They extend existing knowledge by showing that women who continued tamoxifen were more likely to experience MBD decline compared with discontinuers. They also reported a chemotherapy-associated MBD decline among premenopausal women. Though the relation of MBD decline with prognostic outcomes was not evaluated, these present findings suggest that its assessment holds promise as a biomarker of adjuvant tamoxifen adherence.

A persistent clinical concern is poor adherence associated with tamoxifen use (5), partly due to adverse side effects. This is one of few studies to address the potential impact of tamoxifen adherence and discontinuation on MBD decline. The authors utilized linked prescription records from the Swedish Prescribed Drug Register to crudely define tamoxifen-prescribed patients as “continuers” or “discontinuers” based on whether tamoxifen

was dispensed within 180 days before the patient's follow-up mammogram. However, as the authors appropriately acknowledged, dispensed tamoxifen does not equate to consumption. The authors also note that sample size limitations precluded analyses of possible effects of therapy switching and tamoxifen duration on MBD decline. Little is known about the persistence of MBD declines over time or whether there is a rebound effect upon tamoxifen cessation, particularly before the prescribed clinical course is completed. We previously reported that MBD decline observed 1 year after tamoxifen initiation persisted over 5 years (6), with no differences by treatment duration, though sample size was limited. A recent study noted slight increases in MBD with tamoxifen discontinuation (7). Further, not all patients who undergo tamoxifen therapy experience MBD decline (4,6,8–12). Therefore, future efforts to comprehensively characterize patterns of MBD fluctuation associated with continuation and discontinuation of tamoxifen in relation to breast cancer risk and prognostic outcomes will be essential to clearly understand the translational implications of monitoring MBD decline.

A better understanding of underlying mechanisms that accelerate tamoxifen-associated fibroglandular tissue changes, as reflected radiologically in MBD, is needed. For example, it is plausible that women who do not efficiently metabolize tamoxifen could fail to demonstrate MBD decline or treatment benefit. Translation of findings may be accelerated by exploring therapeutic agents that have a more favorable benefit/risk ratio, such as 4-hydroxytamoxifen topical gel, an active tamoxifen metabolite (13). Ongoing clinical studies collecting pre- and post-intervention breast images and tissue samples will be instrumental in deciphering the biological mechanisms driving MBD decline.

With improving strategies for identifying women at elevated risk of breast cancer development (14,15), accompanied by an

increasing population of breast cancer survivors (16), the observed findings highlight opportunities for characterizing MBD change as a surrogate of tamoxifen adherence for primary and secondary breast cancer prevention. In the chemopreventive setting, where tamoxifen uptake is low (17), MBD decline might be used as a tool to monitor risk and encourage adherence. Among breast cancer survivors, MBD decline may have important implications for monitoring tamoxifen effectiveness and risk of contralateral breast cancer (CBC). Recent findings from the WECARE Study of women younger than 55 years at first breast cancer diagnosis showed that elevated postdiagnosis MBD was associated with increased CBC risk (18). Additionally, both tamoxifen and chemotherapy were statistically significantly associated with MBD decline, and MBD declines of 10% or more within 4 years following the first diagnosis were marginally associated with reduced CBC risk (18).

Although most investigations of MBD change have focused on tamoxifen, Eriksson and colleagues also examined influences of aromatase inhibitors (AI), chemotherapy, and radiotherapy. The observed lack of association between AI use and MBD decline is similar to two prior studies (19,20). However, the results conflict with a recent report that used automated software to detect volumetric MBD declines among breast cancer cases using either tamoxifen or AIs compared with untreated women without breast cancer (21). Studies examining MBD decline in relation to AIs are particularly challenging given the low baseline MBD among postmenopausal women, among whom AIs are primarily indicated. Eriksson and colleagues observed MBD declines associated with chemotherapy, but not radiotherapy, consistent with the WECARE Study findings (18). It seems likely that MBD declines following chemotherapy among premenopausal women are related to estrogen deprivation associated with chemotherapy-induced menopause. Whether there are MBD changes in the contralateral breast within radiotherapy fields of the index cancer is unknown. Additional investigations are warranted to confirm whether MBD declines attributed to therapies other than tamoxifen are associated with improved breast cancer outcomes.

Although visual determination of MBD decline has been predictive of tamoxifen effectiveness (8,11), computerized tools, such as the STRATUS breast density assessment software employed in the present report, enable alignment of serial images to facilitate objective and reliable quantitative measures of MBD and its changes (22). Most studies, including the present report, have evaluated MBD decline from mammograms obtained several years posttamoxifen initiation. Nonionizing 3-D imaging modalities, such as whole breast ultrasound tomography (23) and breast MRI (24), may offer advanced opportunities to sensitively assess early density changes at shorter intervals, particularly among younger women. The growing development and availability of automated techniques for measuring MBD holds promise for the application of such tools in the clinic (25).

In summary, identifying noninvasive methods for monitoring tamoxifen effectiveness and for promoting adherence is an urgent, unmet clinical need. This investigation confirms associations between tamoxifen therapy and MBD decline and further emphasizes the need for expanded investigations of its potential as a biosensor of tamoxifen adherence and effectiveness.

Funding

This work was supported in part by the Intramural Research Program of the National Institutes of Health, National

Cancer Institute, Division of Cancer Epidemiology and Genetics (Bethesda, MD), and by the Health Research Board of Ireland, Cancer Prevention Fellowship Programme Reintegration Grant 2013 (CPFPR-2013-1).

Notes

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The authors have no disclosures to declare.

References

- Eriksson L, He W, Eriksson M, et al. Adjuvant therapy and mammographic density changes in women with breast cancer. *JNCI Cancer Spectr*. 2018;00(0):pky071.
- Mullooly M, Pfeiffer RM, Nyante SJ, et al. Mammographic density as a biosensor of tamoxifen effectiveness in adjuvant endocrine treatment of breast cancer: opportunities and implications. *J Clin Oncol*. 2016;34(18):2093–2097.
- Shawky MS, Martin H, Hugo HJ, et al. Mammographic density: a potential monitoring biomarker for adjuvant and preventative breast cancer endocrine therapies. *Oncotarget*. 2017;8(3):5578–5591.
- Li J, Humphreys K, Eriksson L, et al. Mammographic density reduction is a prognostic marker of response to adjuvant tamoxifen therapy in postmenopausal patients with breast cancer. *J Clin Oncol*. 2013;31(18):2249–2256.
- Murphy CC, Bartholomew LK, Carpentier MY, et al. Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: a systematic review. *Breast Cancer Res Treat*. 2012;134(2):459–478.
- Nyante SJ, Sherman ME, Pfeiffer RM, et al. Longitudinal change in mammographic density among ER-positive breast cancer patients using tamoxifen. *Cancer Epidemiol Biomarkers Prev*. 2016;25(1):212–216.
- Kim WH, Cho N, Kim YS, et al. Mammographic density changes following discontinuation of tamoxifen in premenopausal women with oestrogen receptor-positive breast cancer. *Eur Radiol*. 2018;28(8):3176–3184.
- Cuzick J, Warwick J, Pinney E, et al. Tamoxifen-induced reduction in mammographic density and breast cancer risk reduction: a nested case-control study. *J Natl Cancer Inst*. 2011;103(9):744–752.
- Cuzick J, Warwick J, Pinney E, et al. Tamoxifen and breast density in women at increased risk of breast cancer. *J Natl Cancer Inst*. 2004;96(8):621–628.
- Kim J, Han W, Moon HG, et al. Breast density change as a predictive surrogate for response to adjuvant endocrine therapy in hormone receptor positive breast cancer. *Breast Cancer Res*. 2012;14(4):R102.
- Ko KL, Shin IS, You JY, et al. Adjuvant tamoxifen-induced mammographic breast density reduction as a predictor for recurrence in estrogen receptor-positive premenopausal breast cancer patients. *Breast Cancer Res Treat*. 2013;142(3):559–567.
- Nyante SJ, Sherman ME, Pfeiffer RM, et al. Prognostic significance of mammographic density change after initiation of tamoxifen for ER-positive breast cancer. *J Natl Cancer Inst*. 2015;107(3).
- Lee O, Page K, Ivancic D, et al. A randomized phase II presurgical trial of dermal 4-hydroxytamoxifen gel versus oral tamoxifen in women with ductal carcinoma in situ of the breast. *Clin Cancer Res*. 2014;20(14):3672–3682.
- Choudhury PP, Wilcox A, Brook M, et al. Comparative validation of breast cancer risk prediction models and projections for future risk stratification. *bioRxiv* 440347. doi:10.1101/440347.
- van Veen EM, Brentnall AR, Byers H, et al. Use of single-nucleotide polymorphisms and mammographic density plus classic risk factors for breast cancer risk prediction. *JAMA Oncol*. 2018;4(4):476–482.
- Rosenberg PS, Barker KA, Anderson WF. Estrogen receptor status and the future burden of invasive and in situ breast cancers in the United States. *J Natl Cancer Inst*. 2015;107(9).
- Smith SG, Sestak I, Forster A, et al. Factors affecting uptake and adherence to breast cancer chemoprevention: a systematic review and meta-analysis. *Ann Oncol*. 2016;27(4):575–590.
- Knight JA, Blackmore KM, Fan J, et al. The association of mammographic density with risk of contralateral breast cancer and change in density with treatment in the WECARE study. *Breast Cancer Res*. 2018;20(1):23.
- Vachon CM, Ingle JN, Suman VJ, et al. Pilot study of the impact of letrozole vs. placebo on breast density in women completing 5 years of tamoxifen. *Breast*. 2007;16(2):204–210.
- Vachon CM, Suman VJ, Brandt KR, et al. Mammographic breast density response to aromatase inhibition. *Clin Cancer Res*. 2013;19(8):2144–2153.
- Engmann NJ, Scott CG, Jensen MR, et al. Longitudinal changes in volumetric breast density with tamoxifen and aromatase inhibitors. *Cancer Epidemiol Biomarkers Prev*. 2017;26(6):930–937.

22. Eriksson M, Li J, Leifland K, et al. A comprehensive tool for measuring mammographic density changes over time. *Breast Cancer Res Treat.* 2018;169(2):371–379.
23. Sak M, Duric N, Littrup P, et al. Using speed of sound imaging to characterize breast density. *Ultrasound Med Biol.* 2017;43(1):91–103.
24. Chen JH, Chang YC, Chang D, et al. Reduction of breast density following tamoxifen treatment evaluated by 3-D MRI: preliminary study. *Magn Reson Imaging.* 2011;29(1):91–98.
25. Sak MA, Littrup PJ, Duric N, et al. Current and future methods for measuring breast density: a brief comparative review. *Breast Cancer Manag.* 2015;4(4):209–221.