Invited Commentary | Oncology

A Call for Improved Breast Cancer Screening Strategies, Not Only for Women With Dense Breasts

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The study by Narumi-Harada et al is a secondary analysis of the Japan Strategic Anti-cancer Randomized Trial (J-START) cohort. J-START was the first randomized clinical trial powered to investigate the utility of supplemental ultrasonography for breast cancer screening, not only in terms of its diagnostic accuracy (ie, cancer detection rates and positive predictive values), but also to determine its oncologic efficacy. Oncologic efficacy of screening should ideally be evaluated by comparing mortality rates as an outcome. However, assessing mortality rates requires decades of follow-up, which means that the results of today’s screening studies would be available only in the far future, at a time when today's technology will most likely be outdated anyway. Therefore, the efficacy of new screening methods is best evaluated by assessing the rate with which screening fails—that is, the interval cancer rate and/or the fraction of cancers that are detected when they are already at a locally advanced or metastatic stage as proxies for the actual end point, breast cancer–related mortality.

The J-START study found that in Japanese women undergoing routine breast cancer screening, supplemental ultrasonography helped reduce interval cancer rates and the rate of late-stage disease and, thus, helped reduce breast cancer–related mortality. The secondary analysis was done to determine whether women's breast density would modulate these results. Surprisingly, the authors found that the contribution of ultrasonography to early diagnosis of breast cancer in Japanese women did not depend on breast density. This is noteworthy because the current narrative regarding supplemental screening of breast cancer in Western countries says that it is needed only for women with dense breasts.

The female breast is composed of fibroglandular and fat tissue in quite variable relative amounts; like many other biological features, the distribution of fibroglandular vs fat tissue components follows a bell-shaped curve. The more fibroglandular tissue a breast contains, the denser the tissue appears on the mammogram. This is because the fibroglandular tissue causes a strong attenuation of x-rays and, thus, appears white on mammograms, similar to breast cancer; a breast cancer may thus be hidden or masked by overprojecting fibroglandular tissue. Women's individual breast density is determined mainly by genetic factors, with a modulating effect by endogenous or exogenous hormones. Accordingly, breast density may change over a woman’s lifetime; it is usually somewhat denser in young, premenopausal women and may become somewhat less dense after menopause.

In addition to its masking effect, breast density has also been established as a factor independently associated with the risk of breast cancer development. The risk of breast cancer among women with extremely dense breasts is approximately double that among women with nondense breasts, and women with extremely dense breasts have a 4 to 6 times higher risk of breast cancer than do women with fatty breasts. In essence, women with dense breasts undergoing regular mammographic screening face an increased risk of a late diagnosis of breast cancer and, thus, of premature death from breast cancer. Therefore, in the US, women must be informed about their individual breast density and about the diagnostic and prognostic implications of it. Breast imaging societies recommend supplemental screening in these women to compensate for the weaknesses of mammography. Imaging methods...
used for such supplemental screening include breast ultrasonography and breast magnetic resonance imaging.

In the J-START study, ultrasonography was used for screening for women aged 40 to 49 years, regardless of breast density. The rationale was the fact that, although breast cancer is the most frequent type of cancer in the female population in Japan as in the US or Europe, Japanese women differ in several aspects from the average Western screening cohort.

First, the breast density distribution of Japanese women is skewed toward higher breast densities compared with the distribution seen in US or European women. Second, the age at which the peak incidence of breast cancer is observed is skewed toward younger ages; the peak incidence in Japanese women is among premenopausal women aged 40 to 49, whereas in the US and Europe, the peak incidence is among postmenopausal women aged 60 to 69 years. Because premenopausal women tend to have denser breasts than postmenopausal women, the younger age of the target screening cohort will add to ethnic differences associated with higher breast density. The average Japanese woman with breast cancer will, therefore, be younger and have a higher breast density than the average woman with breast cancer in the US or Europe.

In view of the differences between Japanese and Western women, the question arises whether the results of J-START—that supplemental nonmammographic imaging improves breast cancer detection independently of breast density—can be transferred to Western or European screening cohorts. There is evidence to suggest that the answer is yes.

First, although the J-START cohort could be considered an enriched cohort regarding breast density, with 58% of women having dense breasts vs 42% with nondense breasts, the density distribution is only gradually, and not fundamentally, different from that observed in US or European cohorts, where this rate is approximately 43% to 47% vs 53% to 57%, or Chinese cohorts with a rate of 49% vs 51%. Second, the current J-START results are indeed in good agreement with results published in Western screening cohorts. Although the majority of average-risk screening studies conducted in Western cohorts focus on the use of supplemental imaging in women with dense breasts, a handful of studies have been published on cohorts that pursued a similar design as J-START; in other words, they investigated the utility of supplemental, nonmammographic screening in women irrespective of their breast density and/or they provided information on the breast density distribution of women whose cancers had been detected by supplemental, nonmammographic screening alone. The results of these studies are fairly concordant in that the distribution of breast densities of the subcohort of women whose cancers were detected by supplemental imaging only was similar to the distribution of breast densities observed in the respective full cohort. In other words, supplemental ultrasonography or magnetic resonance imaging detected additional cancers in women across all density categories. This finding, however, suggests that with mammographic screening, underdiagnosis of breast cancer (defined as failure to detect relevant breast cancer early enough) occurs not only in women with dense breasts, but also in those with nondense tissue.

Accordingly, this study on Japanese women, as well as the results of studies on supplemental screening conducted in the Western world, suggest that breast density is not the only factor that explains why prognostically important breast cancer is missed by mammographic screening. For Japan, this means that it is prudent to continue with the J-START concept and recommend supplementary ultrasonography screening for all women in the target age group. For the Western world, this should be taken as reminder of the fact that there is still a substantial clinical need to improve breast cancer screening in general, not only for women with dense breasts.

The current focus on testing and implementing improved screening methods for women with dense breasts is justifiable because this subset of women is clearly underserved by mammographic screening alone. However, this is only a starting point. Despite decades of mammographic screening, breast cancer continues to be one of the major causes of cancer death in women overall, not only in women with dense breasts. Thus, the results of the J-START study should remind us of the fact that there is a need for research on improved screening strategies also for women with nondense breasts.
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