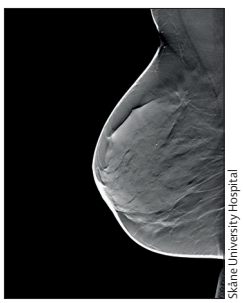
Tomosynthesis in breast screening: great expectations?



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Digital breast tomosynthesis, also known as three-dimensional mammography, has been under investigation as a replacement for or complement to two-dimensional (2D) digital mammography in breast cancer screening for some years, with several prospective, population-based trials reporting increased cancer detection.[1] So far, published studies have been of paired design, in which each woman is her own control—ie, imaged with both digital mammography and digital breast tomosynthesis, read and reported in separate reading groups with either stand-alone digital breast tomosynthesis, or digital breast tomosynthesis in combination with digital mammography or so-called synthetic digital mammography in the digital tomosynthesis group. The paired study design is efficient when used to assess screening performance measures such as percentages of cancer detection and recall. Even if early screening performance measures indicate increased breast cancer detection with digital breast tomosynthesis, whether this design translates into lower proportions of interval cancer and improved long-term reduction in breast cancer mortality, compared with 2D mammography screening, should be elucidated. This assessment cannot be done in a paired study because all women undergo both techniques. Randomised controlled trials such as the To-Be trial[2] by Solveig Hofvind and colleagues, reported *The Lancet Oncology*, are therefore needed. Breast cancer mortality as an endpoint requires large numbers of women, multiple sites, and extended follow-up, and policy decisions are unlikely to wait a decade; therefore, a potential reduction in the proportions of interval cancer is an important surrogate measure.[3]

Hofvind and colleagues' conclusion that "digital breast tomosynthesis and synthetic 2D mammogram is not significantly different from standard digital mammography as a screening tool for selected breast cancer screening outcome measures in a population-based screening programme," raises the question of whether this is the beginning of the end of digital breast tomosynthesis screening, or whether we should we consider these results in context and learn from them. Screening with digital breast tomosynthesis comes at a higher cost and longer reading time, but with the expectation that digital breast tomosynthesis cancer detection will be much better than 2D mammography. The modest increase in cancer detection with digital breast tomosynthesis in the To-Be trial, by contrast with the prospective paired trials, requires explanation. Hofvind and colleagues suggest the possibly diminished statistical power, use of a first-generation digital breast tomosynthesis and synthetic digital mammography unit, and radiologists with little digital breast tomosynthesis experience as plausible explanations. Because digital breast tomosynthesis is a fairly new technique with poineering trials starting around 2012, radiologists were inexperienced with this technique also in earlier trials,[4,5] so perhaps the inexperienced radiologists are not the main factor contributing to the lower detection rate in the To-Be trial. Commercial digital breast tomosynthesis systems are quite different, with variation possible in the sweep angle, number of projections, dose distribution, and image reconstruction methods.[6] In addition to the potential differences in the technology, human readers and their perception—frequently considered the weakest link in radiology—might also be a potential cause of the modest increase in cancer detection. From mammography and other areas in radiology, we know that perception is crucial for human detection and varies with experience.[7] How the images are presented to the screen-reading radiologist and how they then search the images (image volumes in digital breast tomosynthesis) for pathology is also important. The reader protocol in To-Be is quite extensive, starting with the synthetic 2D mammogram, followed by thicker tomosynthesis slices (10 mm slabs), and then the thinner original 1 mm tomosynthesis slices, all in two projections. Synthetic 2D mammograms have been shown to be as good as digital mammography in conjunction with digital breast tomosynthesis.[4] Synthetic mammograms do not contain as much information as a tomosynthesis stack and should be used as an overview or for comparison with previous digital mammography, not for sole diagnosis. Furthermore, slabs that are too thick (ie, 10 mm) might have a negative effect on sensitivity.[8] Thus, the order of the reading and the type of images used might have had an effect on the sensitivity and specificity. Additionally, we do not know to what extent the radiologists searched the full tomosynthesis volume (1 mm slices). If regions of the breast containing cancers that would be visible on digital breast tomosynthesis do not register as suspicious

on synthetic 2D mammograms, there is a risk of a kind of satisfaction of search (ie, the radiologist not searching those parts of the tomosynthesis stack rigorously).[7] In future, the combination of a radiologist and artificial intelligence might help to avoid such effects.

Encouraging findings from the To-Be trial are the lower proportion of recall and lower consensus for women screened with digital breast tomosynthesis versus digital mammography, and the higher positive predictive value for recalls for digital breast tomosynthesis compared with digital mammography, in concordance with many of the retrospective digital breast tomosynthesis studies done in the USA.[1] These are important outcomes in a screening scenario, and are contrary to most of the paired trials in which recall was increased with digital breast tomosynthesis; however, the baseline recall percentage with digital mammography was lower in these trials (2·5%[5] and 2·6%[9]) compared with the To-Be trial (4·0%) and the US studies.[1]

The To-Be trial is the first completed randomised, controlled trial with digital breast tomosynthesis, embedded in a real-world, population-based screening programme, and is an important contribution to the understanding and evidence of early implementation of digital breast tomosynthesis in breast screening. Given that this is the first randomised trial of this technology, it has the potential to contribute important future information on interval cancers. The study illustrates the complex interplay between new techniques and human readers in high-volume screening, and the challenges we will face in a possible future implementation phase of a new technology. The To-Be trial is probably not the beginning of the end of digital breast tomosynthesis screening, rather it heralds the arrival of randomised, controlled trials of tomosynthesis screening, with several now in progress.[10]

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I was involved as an external consultant for the planning of the To-Be trial in the initial phase of the protocol drafting. I have not since been involved at any time during the trial, analysis, or writing of the Article. I have received speaker's fees and travel support from Siemens Healthcare. I have a patent issued from the US Patent Office (US 9 833 203).

1 Marinovich ML, Hunter KE, Macaskill P, Houssami N. Breast cancer screening using tomosynthesis or mammography: a meta-analysis of cancer detection and recall. *J Natl Cancer Inst* 2018; **110:** 942–49.
2 Hofvind S, Holen ÅS, Aase HS, et al. Two-view digital breast tomosynthesis versus digital mammography in a population-based breast cancer screening programme (To-Be): a randomised, controlled trial. *Lancet Oncol* 2019; published online May 8. http://dx.doi.org/10.1016/S1470-2045(19)30161-5.
3 Houssami N, Lång K, Hofvind S, et al. Effectiveness of digital breast tomosynthesis (3D-mammography) in population breast cancer screening: a protocol for a collaborative individual participant data (IPD) meta-analysis. *Transl Cancer Res* 2017; **6:** 869–77.
4 Tirada N, Li G, Dreizin D, et al. Digital breast tomosynthesis: physics, artifacts, and quality control considerations. *Radiographics* 2019; **39:** 413–26.
5 Ganesan A, Alakhras M, Brennan PC, Mello-Thoms C. A review of factors influencing radiologists' visual search behaviour. *J Med Imaging Radiat Oncol* 2018; **62:** 747–57.
6 Skaane P, Bandos AI, Eben EB, et al. Two-view digital breast tomosynthesis screening with synthetically reconstructed projection images: comparison with digital breast tomosynthesis with full-field digital mammographic images. *Radiology* 2014; **271:** 655–63.
7 Iotti V, Giorgi Rossi P, Nitrosi A, et al. Comparing two visualization protocols for tomosynthesis in screening: specificity and sensitivity of slabs versus planes plus slabs. *Eur Radiol* 2019; published online Feb 8. DOI:10.1007/s00330-018-5978-x.
8 Zackrisson S, Lang K, Rosso A, et al. One-view breast tomosynthesis versus two-view mammography in the Malmö Breast Tomosynthesis Screening Trial (MBTST): a prospective, population-based, diagnostic accuracy study. *Lancet Oncol* 2018; **19:** 1493–503.
9 Skaane P, Bandos AI, Niklason LT, et al. Digital mammography versus digital mammography plus tomosynthesis in breast cancer screening: the Oslo Tomosynthesis Screening Trial. *Radiology* 2019; **291:** 23–30.
10 Pattacini P, Nitrosi A, Giorgi Rossi P, et al. Digital mammography versus digital mammography plus tomosynthesis for breast cancer screening: the Reggio Emilia tomosynthesis randomized trial. *Radiology* 2018; **288:** 375–85.

Genetics to epigenetics: targeting histone deacetylases in hormone receptor-positive metastatic breast cancer

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During the past decade, the use of combination targeted therapies for hormone receptor-positive, HER2-negative metastatic breast cancer has increased substantially. Besides approval of mTOR and CDK4 and CDK6 inhibitors in combination with endocrine therapy as second-line or later treatment,[1,2] positive results have been reported[3] with an α-specific PI3K inhibitor, alpelisib, in combination with endocrine therapy for patients with hormone receptor-positive, HER2-negative, metastatic breast cancer who have *PIK3CA* mutations. In addition to genetic alterations, epigenetic modification via histone deacetylases (HDACs) is another putative mechanism by which gene expression patterns can be changed, leading to cellular growth and proliferation.[4] In preclinical models of endocrine-resistant breast cancer, HDAC inhibition can restore oestrogen receptor dependency on, and