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Should tomosynthesis replace mammography for breast cancer screening?

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A decade has passed since the first prospective trials of digital breast tomosynthesis showed that this mammography technology increased cancer detection rate (CDR) compared to digital mammography[1;2]. A large body of evidence, comprising prospective non-randomised and retrospective studies[3], has since evolved however evidence from randomised controlled trials (RCTs) has been scarce. Heindel and colleagues report TOSYMA[4], the largest of three RCTs providing evidence on breast tomosynthesis versus mammography screening[4-6], a multi-centre trial embedded in the German population-screening program. The investigators persevered with TOSYMA despite the COVID-19 pandemic stalling recruitment to marginally below the revised sample size in their adaptive design[4]. TOSYMA showed that tomosynthesis (with synthetic-2D imaging) significantly increased CDR in participants aged 50-69 years, specifically increasing *invasive* cancer detection by an 'extra' 2.3 cancers per 1000 screens[4]. This aligns with findings from the recently reported Italian RCT which also showed significantly increased CDR from tomosynthesis (with acquired rather than synthetic-2D)[6]. Although the remarkable increase in CDR from tomosynthesis in both RCTs contradicts the earliest RCT from BreastScreen Norway[5], it comes as no surprise based on the collective evidence: higher CDR for tomosynthesis has been reported in comparative studies of tomosynthesis and mammography in organised population-based programs in several countries[3;7;8]. Meta-analyses confirm that tomosynthesis increases CDR across age-group and breast density strata and show that increased CDR is most evident in biennial screening practice[3;7].

Mammography screening is the most effective cancer control strategy for breast cancer; alongside the benefit of mortality reduction, exist the harms of recall for further testing (representing mostly false-positive screens) and overdiagnosis[9]. Tomosynthesis is unlikely to add harm from excessive recall, on the contrary, it reduces recall where mammography has high recall rates, as shown in studies from the USA where annual screening is common practice[3]. Evidence from the RCTs, all implemented in organised programs where recall is relatively low, shows tomosynthesis has no effect on recall or could reduce it[4-6]. However, little is known about how tomosynthesis impacts breast cancer mortality or overdiagnosis, therefore evidence on surrogate outcomes for screening benefit (versus harms) will be sought before tomosynthesis can be widely recommended instead of mammography in screening policy. Interval breast cancers diagnosed in the inter-screen interval, and advanced cancer rates at subsequent screening rounds, are intermediate surrogates for screening effectiveness. A reduction in their rates would signal a beneficial effect on *progressive cancers* also indicating that tomosynthesis does not preferentially increase overdiagnosis. A reduction in interval cancer rates following the increased CDR of the magnitude achieved with tomosynthesis screening[3;4;6], would provide critical evidence that this enhanced screen-detection

was detecting cancers that would have clinically progressed within 2 years of screening, ultimately extending the mortality benefit from breast screening.

Although TOSYMA is yet to report on that key endpoint of interval cancer rate[4], the Italian RCT found no difference in interval cancer rate at follow-up, a disappointing result given the increased CDR in the trial's tomosynthesis arm[6]. An individual participant data meta-analysis of prospective studies found tomosynthesis screening had little impact on interval cancer rate despite significantly increasing CDR[10]. The Norwegian RCT also did not find a difference in interval cancers at follow-up of screened women, however this was expected given the proportion of screen-detected cancer did not differ between those who received tomosynthesis and those who received mammography in that RCT[5]. Only the Malmö trial found a reduction in interval cancer rate from tomosynthesis screening, in the context of a non-randomised trial with matched controls assembled after trial completion[8].

In the absence of sufficient evidence of an effect on interval cancer rate, and no evidence on long-term outcomes, the concern that tomosynthesis could be over-detecting or adding lead time without improving long-term outcomes will deter population screening programs from replacing mammography with tomosynthesis. The increased screen-reading time for tomosynthesis, roughly double that of mammography in TOSYMA[4], whilst not the only barrier to adoption, represents a real-world resourcing challenge for screening programs tasked with screening a considerable proportion of the female population.

At present, improved screening performance metrics (cancer detection, recall) are unlikely to be the sole impetus for widespread transitioning to tomosynthesis in programmatic screening. However, these metrics have supported its adoption as replacement to digital mammography in many radiology services in developed health systems; the reduced recall observed in annual screening has accelerated the shift to tomosynthesis particularly in the USA, and this is likely happening elsewhere. Strategically, population-based breast screening programs need to pro-actively prepare for the possibility of a transition to tomosynthesis through program-embedded trials to accelerate evidence on key screening outcomes, and to identify the most appropriate model to use tomosynthesis, which may entail novel ways of screen-reading and reimagining the double-reading process[8]. This may require multi-centre and possibly multi-national efforts to establish whether tomosynthesis improves health outcomes for women compared to mammography screening.

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