

The mammography debate: the senior years

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Facts do not go away while scientists debate rival theories for explaining them.

— Stephen Jay Gould, *Hen's Teeth and Horse's Toes*

Pistols at Dawn: A Reader's Guide to a Recent Exchange

The recent series of important exchanges within the long-lived mammography debate in the pages of this journal were triggered by the publication in 2014 of the 25-year follow-up of the Canadian National Breast Screening Study (CNBSS) incidence and mortality data¹, putting that Canadian randomized controlled trial (RCT) and its authors once again at the centre of a storm of criticism and subsequent defense. The most recent stimulus for the exchanges began with Dr. Steven Narod's detailed defense of the trial's findings in a Countercurrents Series paper², drawing a sustained response from Dr. Martin Yaffe and a brief rebuttal by Narod in a Point-Counterpoint exchange^{3,4}, with some of the issues taken up independently by Dr. Dan Kopans⁵. Yaffe then, in his response⁶ to an unrelated paper⁷, took up one of the most contentious issues, namely, the randomization process—especially as to observed imbalances of advanced cancers and survival in the screened and control arms. Chapter Two of the debate opens in this issue with Dr. Anthony Miller's response⁸ to Yaffe, and then Yaffe's own response⁹ to Miller, randomization again at centre stage.

The Issue of Random Allocation Imbalance

The relative merits of the reasoning in these two counter-narratives of Miller and Yaffe can be argued, but there are larger issues of interest here that put the exchange into a wider and more consequential perspective. That there is an imbalance favouring more palpable breast cancers in the mammography arm is not in dispute, and Yaffe makes a compelling case for how quite modest perturbations in the balance of advanced cancer allocation can engender consequentially large increases in the associated hazard ratios. But Miller and the Canadian trialists candidly acknowledge the imbalance, seeking to provide a corrective in the form of exclusion from consideration of prevalence-detected cancers (detected in the first screening year). The difficulties, however, could be deeper still: None of the other seven screening RCTs manifested an excess of advanced cancers in the study group compared with the control group. In addition, second-year-detected cancers not previously identified by mammographic screening (possibly because of suboptimal quality of mammography

in the first year) remain unadjusted, still leaving 23% more cancers identified in the mammography arm than in the control arm¹⁰, which appears beyond the reach of chance alone. The more profound scope of the problem is further suggested by the fact that even if, more aggressively, the imbalances of *both* the first and second years are discounted, the imbalance between the cohorts remains durable at 15% excess in the screening cohort across the remaining incidence years (years 3 through 5)¹⁰. So the excess, and the anomaly, remains.

The Issue of Forward Relevance

Beyond the imbalance, however, a time-bounded limit of applicability must be recognized for all of the now decades-old screening RCTs beyond just the CNBSS, rendering them of limited—but not null—explanatory power and relevance projected forward into the modern epoch of mammography.

First, of the seven population-based RCTs [CNBSS was not a population-based trial, the participants being self-selected; it limited screening to 3–4 years after study entry (maximum 5 annual rounds) and involved participants whose ages ranged narrowly from 40 to 59 years (in whom the breast cancer incidence is typically lower)], six used only 1 mammographic view per breast instead of the current 2-view standard¹¹, causing significant underestimation (2-view screening can dramatically increase cancer detection). Moreover, the CNBSS is, definitionally, not strictly a screening trial (diagnostic assessment of palpable masses being outside the borders of breast cancer screening limited to solely asymptomatic women).

Second, of the seven population-based RCTs (the exception in both cases being the HIP trial¹²), six used supra-annual screening intervals, despite the superior benefits from annual screening. The U.S. Preventive Services Task Force guidelines¹³ still recommend biennial screening despite a 70% additional improvement in survival outcomes under annual screening, as found and acknowledged in their own model. The early mortality reduction from annual mammography screening in women 40–49 years of age in general, regardless of breast density, has been robustly confirmed by RCT in the 17-year follow-up of the U.K. Age trial¹⁴.

^a The No Surrender Breast Cancer Foundation is a U.S.-based 501(c)3 not-for-profit organization providing high-quality critically reviewed and appraised information and guidance to the breast cancer community.

Third, all the RCTs used insufficient screening rounds (although the Malmö Trial¹⁵ continued screening through 10–11 years of follow-up). A significant screening-related mortality reduction emerges only once a requisite delay threshold is passed (the 6th year in the Malmö Trial), and in general, significant mortality-reduction benefits from screening emerge only after some 5–8 years after screening commencement, the study and control group mortality curves not even beginning to separate significantly before 4–5 years from screening initiation^{11,14}.

Fourth, most trials failed to differentiate between screening invitation and screening attendance, generating a continued distortive influence from reliance on number needed to invite (which necessarily provides lower estimates of mortality benefit) rather than on the actual number needed to screen.

Back to the Future

Finally, as previously argued⁷, and as the above considerations reinforce, it is imperative to move beyond the mammography debate:

1. To acknowledge the strengths, but also the considerable limitations of early-era screening RCTs, as suggested above.
2. To accept the strong relevance of observational and case-control screening program data.
3. To recognize that any claimed harms of screening must be weighed against the real harms of its omission^{16,17}.
4. To concede that mortality reduction is not realistically the only endpoint for deployment of mammographic screening. Real benefits beyond lives saved or prolonged must be weighed in assessing the true benefit-harm trade-offs of continued screening: freedom from symptomatic cancer; reduction of treatment-related morbidities; wider management choices for the patient, including chemoprevention; favourable surgical downstaging; and a more favourable natural history of the cancer, including fewer late-stage cancers; among many others.
5. To recognize that seemingly large differences in critical screening estimates—of lives saved and of overdiagnosis or overtreatment, most critically—are in many cases more apparent than real, and when subjected to well-defined processes of normalization (as previously discussed^{7,18}) might reveal more convergence than disputants have realized or acknowledged, and that such normalization significantly reduces the number needed to invite or screen to levels that would be considered acceptable in benefit-harm balance.
6. To achieve a true consensus of experts, past the well-intentioned but ill-advised failed experiment of the U.S. Preventive Services Task Force, whose panel proudly but disastrously does not include experts in breast cancer imaging or treatment (witness their critical misunderstanding of confidence intervals in another of their guidelines¹⁹, failing Evidence-Based Medicine 101), what is needed is a panel of the Anthony Millers and the Martin Yaffes, the Steven Narods and the Dan Kopans, plus Cornelia Barnes, László Tabár, Philippe Autier, Stephen Duffy, Donald Berry, and

Stephen Feig, among other pro- and anti-screening disputants. A hard-fought and aggressively moderated consensus—the core of what all can agree on and commit to—emerging from that panel ... *that* would be worth having.

7. To shift focus, research, and intelligence to more constructive efforts to improve breast cancer screening that avoid the limitations of mammography-based screening. Those efforts range from the emerging abbreviated breast magnetic resonance imaging (MRI) technologies²⁰; to the increasingly rapidly deployed technologies of digital breast tomosynthesis (as previously discussed^{7,18}), which can reduce false positives while increasing cancer detection; to more sophisticated modelling studies²¹; and to the new *radiomics* (that is, high-throughput extraction and quantitative feature analysis from imaging to generate predictive and prognostic models that relate observed imaging features to phenotypes or genotypes and to imaging biomarkers predictive of malignant progression²²)—all being advances that can significantly mitigate any potential overdiagnosis.
8. To enable and to learn from a newer generation of trials that will materially advance both the state and a deeper, more nuanced knowledge of the benefits of screening mammography. There are several promising examples. By late 2020, preliminary findings from the Women Informed to Screen Depending on Measures of Risk (wisdom) trial (University of California)—a modern-era RCT of screening mammography (yes, screening RCTs will still be launched, and others are in the planning)—are expected to be released. That trial will assess comparative survival outcomes from a risk-tailored approach to breast cancer screening compared with annual mammographic screening, and will, as a modern-era screening RCT, reconfirm mammography's mortality-reductive benefits. The E4112 trial from the Eastern Cooperative Oncology Group and the American College of Radiology Imaging Network will directly address the issue of ductal carcinoma *in situ* overdiagnosis and overtreatment by ascertaining the value of MRI plus the Oncotype DX DCIS Score in the identification of patients with ductal carcinoma *in situ* at sufficiently low risk of recurrence to avoid radiation therapy. The randomized FAST MRI Study in Breast Cancer Survivors (The Ottawa Hospital Research Institute) will explore the benefits of FAST breast MRI⁷ as a screening technique in women with a personal history of cancer (FAST MRI plus annual mammography vs. annual mammography alone). And in connection, the Ultra FAST Breast Magnetic Resonance in Breast Cancer Screening trial (Brugmann University Hospital, Belgium) will explore the benefits of the ultra-FAST streamlined MRI protocol^{7,20} in normal screening populations.

Collectively, the new imaging technologies, plus advances in screening modelling, and the leveraging of insights from both in-progress clinical trials and the new radiomics, will obviate the current limitations of mammographic screening and help to obsolete many of the

not-always productive controversies of the mammography debate, something that should unite screening advocates and critics alike, because we are all, independent of partisan stripe, here to enhance the breast cancer preventive and outcome-improving options and technologies available to best serve the ultimate stakeholder in the debate, screening-eligible women. Perhaps the fog is lifting.

CONFLICT OF INTEREST DISCLOSURES

I have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and I declare that I have none.

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