



Screening mammography: the turning of the tide?

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This issue of *Current Oncology* features a Counter-currents article by Dr. Steven Narod, “Reflections on screening mammography and the early detection of breast cancer”¹, that is accompanied by a commentary from Professor Michael Baum² supporting Narod’s thesis. Indeed, in Baum’s view, Narod’s only error was not to push home the point that the Canadian National Breast Cancer Screening Study (NBSS) is not an outlier among mammography screening studies. He commends Narod for a measured response to the widespread criticism that followed publication of the 25-year follow-up results of the by now notorious NBSS.

It seems as if almost everyone has an opinion on screening mammography. Everyone is entitled to an opinion, of course; but discussions about mammographic screening tend to take on a special, almost unique, quality—which perhaps speaks to the investments (financial, psychological, and career) made by many of the protagonists, which Professor Baum fleetingly mentions as potential conflicts of interest in his editorial. Baum prefers to see the ongoing debate—if that is what it is—as a clash of ideologies. But what are these ideologies that are so opposed?

Essentially, Baum’s argument is that the proponents of screening are not really scientists, in the sense that they do not accept refutation of data by data. He could be right, but I think the more parsimonious and psychologically more plausible explanation is that the aforementioned investments are simply too great: the stakes are too high. That the stakes are high is, in my view, very clear. Breast cancer is a common disease, and if population-based screening mammography is shown to have failed and is therefore no longer offered, billions of dollars would be saved every year in the United States alone³.

Narod contrasts the results of two large trials of mammography (one carried out in Sweden, the two-county study) with the NBSS data. Having read these carefully laid out arguments, I think that most disinterested, but informed, readers will accept

that many of the legion of criticisms that have been placed at the door of the NBSS simply do not hold up to scrutiny. But mud sticks, and so many observers who do not like the results of the NBSS point again and again to the same “flaws.”

One of Narod’s most telling points is that the survival curves for the two arms of the Swedish trial continue to remain separate up to 29 years after the trial was started. That observation is not consistent with any known effect of mammographic screening. It is much more likely that the populations were simply different to start with.

Further discussion of the pros and cons of these two trials is now fairly pointless. There are not much new data to be had, and I can’t see Drs. Kopans and Tabár, on reading Narod’s article, deciding that perhaps the benefits of mammography have, after all, been overestimated. Without new data, we can’t resolve this critical issue. So perhaps we need to stop the current process and actually do some new research to gather the required data.

A recent Perspective article in the *New England Journal of Medicine*⁴ noted the presence of a deep chasm separating women’s views of the likely benefit of mammographic screening and the actual data available. The nongovernmental Swiss Medical Board subsequently determined that women could not make informed decisions about screening without access to more nuanced information. Moreover, the Board felt that the benefits of mammographic screening were likely to be so small that no new screening programs should be introduced and existing programs should be allowed to run down. Their decision caused the expected uproar, but it is interesting to note that the results of a reader poll after a Clinical Decisions article 2 years earlier in the *New England Journal of Medicine*⁵ showed that a clear majority did not think that screening mammography should be started at age 40. Those results are contrary to the recommendation of many breast cancer organizations. But on the basis of these newer findings, it seems to me that the tide has turned, insofar as

there are now enough interested parties prepared to question the benefits of mammography.

One of the points that Narod makes bears some discussion: He sees the problem not in terms of 30-year-old mammography machines in NBSS study, but in 30-year-old thinking about the biology of breast cancer on the part of those who support screening. Logically, it can be seen that, as breast cancers enlarge, the number of cancer cells within them increases, which can provide opportunities for more malignant clones to emerge. Earlier detection will thus prevent those emerging clones from worsening outcomes. This quasi-Halstedian view, that a breast cancer makes a stately progression through biologically distinct and distinguishable stages and that the grade worsens as the tumour enlarges (assumptions that are at the heart of the original explanation of how mammography “works”⁶), are no longer part of mainstream thinking about breast cancer biology. Even ductal carcinoma *in situ* seems to possess many of the molecular changes found in invasive breast cancers, albeit at lower frequencies^{7,8}. It seems as if the “die is cast” fairly early in the life of a breast cancer⁹. Intrinsic subtypes hold true as cancers grow and metastasize¹⁰, and the sojourn time varies from subtype to subtype¹¹. Some breast cancers regress¹². Others grow very rapidly¹³. These are not ideal biologic circumstances for the success of an “across the board” screening program. That conclusion is even borne out by a careful examination of the two-county study data¹⁴. The one group for whom screening mammography would be hoped to work—women between 40 and 49 years of age with a grade III breast cancer (a group likely to contribute disproportionately to the observed mortality from breast cancer)—does not seem to achieve any mortality savings (see Figure 20 in Tabár *et al.*¹⁴). Survival at 16 years from randomization was identical in the invited and screened groups (relative risk: 0.95; 95% confidence interval: 0.55 to 1.64). One wonders if, in fact, the shoe is on the other foot. What has been learned about interpreting screening data from the current understanding of the natural history of breast cancer?

On the other side of the ledger, overdiagnosis has emerged in the past several years as a major issue in breast cancer screening. Quantifying the benefits and harms of mammography make for sobering reading by disinterested parties. If one starts with a sample of 1000 U.S. women 50 years of age, and if those women are screened annually for a decade, fewer than 4 women will avoid a breast cancer death; 3–14 women will suffer the consequences of overdiagnosis; and many hundreds will have at least 1 false alarm¹⁵. Work by Welch and Frankel suggests that women would think differently about mammographic screening for breast cancer if they were made aware of those figures at time of invitation for screening. Using best estimates, only 1 woman in

4 who develop a screen-detected breast cancer will avoid a breast cancer death¹⁶. The other 3 will do just as well, or just as poorly, without screening—or, of more concern, will have been diagnosed with a cancer that was not destined to ever present clinically. In the observational Norwegian study, only one third of the reduction in deaths from breast cancer could be attributed to mammographic screening *per se*¹⁷. Most women with a screen-detected breast cancer are therefore either diagnosed early (but with no effect on outcome) or are overdiagnosed.

We have been here before. Maureen Roberts, director of the Edinburgh breast screening project, died of breast cancer in 1989. While hopeful that mammographic screening would benefit women, she concluded from an analysis of the Edinburgh trial results that it did not. Before she died, she wrote “Breast screening: time for a rethink?” for the *British Medical Journal*¹⁸, concluding, “I feel sad to be writing this; sad because naturally after so many years I am sorry that breast screening may not be of benefit. I am also sad to seem to be critical of the many dear and valued colleagues I’ve worked with over the years, particularly those who have made such a magnificent contribution to the care and welfare of women with breast cancer. But they will recognise that I am telling the truth.”

It is time to work toward a trial of screening mammography that will incorporate variable thresholds, molecular markers, genetic testing, and psychological and physical measures of the effect of overdiagnosis. One of the two authors of the *New England Journal of Medicine* Perspective article discussed earlier, an ethics representative on the Swiss Medical Board, has argued that there is a moral requirement for a randomized controlled trial of mammography¹⁹ based on Welch’s idea of differing detection thresholds. I believe that women will be interested in such a study. But because almost every major U.S. medical organization focusing on breast cancer prevention, diagnosis, or treatment has stated that women should begin undergoing mammography annually from the age of 40 years, will any agency have the courage to fund it?

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CONFLICT OF INTEREST DISCLOSURES

The author has no financial conflicts of interest to declare.

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