RE: “TWENTY FIVE YEAR FOLLOW-UP FOR BREAST CANCER INCIDENCE AND MORTALITY OF THE CANADIAN NATIONAL BREAST SCREENING STUDY: RANDOMISED SCREENING TRIAL”

Some of us engaged in evaluating the efficacy of cancer screening were surprised at the high level of media attention given to a February 2014 report on the null results of a Canadian randomized trial of screening mammography (1) and at the weight given to these results in media summaries. In the article, Miller et al. (1) documented mortality from breast cancer over a 25-year period among 1) women aged 50–59 years who had been randomized either to 5 years of annual screening by means of clinical breast examination or to clinical examination plus mammography and 2) women aged 40–49 years who had been randomized to receive only a single clinical examination or 5 years of annual clinical examination plus screening mammography. Women of all ages in both arms of the trial received instruction in breast self-examination.

Why the surprise? First, the trial was, effectively, an evaluation of the noninferiority of clinical examination alone relative to the combination of clinical examination and mammography. Given that clinical examination has a fair degree of sensitivity in identifying occult breast cancer (2), the magnitude of the potential benefit of screening mammography in this study had to have been considerably smaller than that observed in studies where women in the control arm received either no screening at all or a single screen at the conclusion of the intervention period (3–5). Second, similar null results of this trial obtained using data collected through 11–16 years after program entry had been reported some 12 years earlier (6). Among women who developed screen-detectable breast cancer in the 5 years during which the trial took place, the large majority of breast cancer deaths that were destined to occur would have occurred during the first 11–15 years. Most breast cancer deaths taking place during the final 9–14 years of follow-up would have been among women whose tumors became potentially detectable only after the screening program had ended. Thus, given the absence of any appreciable reduction in breast cancer mortality among women assigned to receive screening mammography through 11–15 years of follow-up, longer follow-up without continued differential screening between women in the 2 arms of the trial could have been expected to produce nothing other than another null result (7).

Perhaps it is understandable that the media wish to present to their listeners/viewers/readership information that is “new” and/or controversial. Cognizant that this goal sometimes (!) can be inconsistent with providing news that is balanced and adequately nuanced, what steps could have been taken by those who conducted and published the research to make its correct interpretation more likely?

First, I believe the authors could have sought to present more completely the integrated results of all relevant studies. In addition to the fair portrayal they provided of the data obtained in their own study and their conclusion (correct, in my view) that “annual mammography does not result in a reduction in breast cancer specific mortality for women aged 40–59 beyond that of physical examination alone” (1), they could have summarized the results of trials (and nonrandomized studies) that contrasted screening mammography with no breast cancer screening.

Second, the investigators could have acknowledged that the results of the extended follow-up of trial participants provided data of limited value. Though the authors conducted their study and described its findings in an exemplary manner, they failed to indicate that the data most likely to have been able to identify a decreased risk associated with a 5-year screening mammography program (if one were present) had been published more than a decade earlier (6). Their recognition of the marginal importance of an analysis that included follow-up beyond 11–15 years could have led to a decision to 1) publish the very long-term follow-up results in a journal less prominent than the British Medical Journal and 2) include a caution to readers regarding the dilution of any true mammography-associated reduction in mortality by the proportionally large number of breast cancer deaths beyond 11–16 years from cancers that were not detectable during the 5 years in which the screening program was operating. In their article, the authors concluded by suggesting that “the value of mammography screening should be reassessed” (1). I believe that the time for such a reassessment was in 2002, following the publication of their 11- to 15-year follow-up data (6)—before the interfering effect of breast cancer cases that became detectable after the conclusion of the screening program.

As scientists, we’re trained to reassess our beliefs in the light of new information. However, information that is new may not be information that is important. I would argue that when weighing the pros and cons of screening mammography, the recently updated data available from the Canadian randomized trial concerning mammography should be accorded little or no weight, beyond that given to the valuable data that this study had already provided.

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REFERENCES
We thank Dr. Weiss for his comments (1). However, we feel that Dr. Weiss is in error over several issues. First, for women aged 40–49 years, the “noninferiority” of the control arm in the Canadian National Breast Screening Study must be interpreted with a recognition that these participants received only an initial breast examination and were taught breast self-examination (2). Thus, after the first screen, the comparison was between mammography and usual care in the community, not regular clinical breast examinations.

Second, the numbers of breast cancer deaths had increased since our previous reports (3, 4), thus substantially narrowing the confidence interval of the estimate of a null effect of mammography. In fact, the main results presented in our recent report (2) relate to the cancers diagnosed during the 5-year screening period. Compared with the previous reports (3, 4), the numbers of breast cancer deaths increased from 138 in the mammography arm and 128 in the control arm to 180 and 171, respectively, in our recent report (2). Further, for all breast cancer deaths, the numbers increased from 212 and 213 in the previous reports to 500 and 505 for the mammography and control arms, respectively. This refutes the claim that nothing has changed in our current report.

Third, the extended follow-up enabled us to estimate the extent of overdiagnosis from mammography with a very long natural history. Our extended follow-up conclusively discounts this possibility.

In his letter (1), Dr. Weiss criticizes us for not reviewing the results of other breast screening trials. In fact, we did mention some of them but felt that it was not up to us to conduct a complete re-review of those findings at this time.

Thus, in our view it is very important that the results of our study, with its unique design, demonstrating no beneficial effect of mammography screening (2), be emphasized, and it seems that others agree with us (8, 9). Indeed, many investigators have failed to recognize the competing effects of screening and improved treatment of breast cancer (10–12). Thus, we renew our call for a reassessment of the value of mammography screening.

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**REFERENCES**


