Miller et al. (1) report on the most recent results of a randomized trial of breast screening in Canada. At 16 years after randomization, there were 107 deaths observed among women randomly assigned to receive annual mammography plus physical examination and 105 deaths among a similar number of women randomly assigned to receive an annual physical examination alone. The authors interpret this to mean that the two methods of screening were equivalent—i.e., that annual physical examination by a trained professional is a viable alternative to annual mammography and should be available to women 50 years old or older. This message has also been highlighted by several media reports covering the publication of the trial results.

If this were a trial of mammography alone versus physical examination alone, this conclusion would be rational. However, if mammography and physical examination were equivalent (but not identical), I would expect the combination of the two to outperform either modality alone. In fact, the combination of mammography plus physical examination outperformed physical examination alone by every measure—except death. The tumors in the mammography arm were smaller, on average, than those detected in the physical examination arm and were more likely to be lymph node negative. Miller et al. present data showing that physical examination advanced the date of diagnosis by 1.5 years but that adding mammography advanced it further by 2.1 years. Surely, if early detection enhances the prospect of cure, a lead time of 3.6 years must be preferable to a lead time of 1.5 years. But this was not found to be the case. The rational interpretation of this dataset is not that the two screening methods were equivalent, but that neither was effective. I believe that researchers should now devote their attention to understanding why this is the case and should pay greater attention to advancing primary prevention.

Steven A. Narod

REFERENCE


NOTE

Correspondence to: Steven A. Narod, M.D., FRCPC, The Centre for Research in Women’s Health, University of Toronto, 790 Bay St., 7th Floor, Toronto, ON, Canada M5G 1N8 (e-mail: steven.narod@swchsc.on.ca).

RESPONSE

We thank Professor Narod for his comments. We agree that one possible explanation for our findings (1) is that neither screening with mammography plus physical examination nor physical examination alone was effective. However, breast cancer mortality may have been reduced in both arms of the trial, but that can only be inferred, since it was deemed unethical to have an unscreened control group.

The trial design was based on the assumption that mammography screening reduced breast cancer mortality in women aged 50–59 years, and the apparent indicators of mammography effectiveness that Professor Narod lists, cited by others as indicating that breast screening is likely to be effective (2,3), were met in the trial. This suggests an alternative explanation for the coexistence of favorable indicators of mammography effectiveness and the lack of breast cancer mortality reduction compared with physical examination only—namely, that the majority of the small (impalpable) cancers detected by mammography represent pseudo-disease or overdiagnosis. Recently, in the context of lung cancer screening, it has been pointed out that overdiagnosis is being ignored (4). In practice, screening with mammography plus physical examination only slightly reduced the number of large breast cancers (20 mm or more in diameter) compared with physical examination alone during the period of screening in the Canadian National Breast Screening Study-2 [114 and 136, respectively (1)] but not the number of lymph node-positive cancers [92 and 86, respectively (5)]. Thus, the “advanced” breast cancers associated with mortality were not affected by the addition of mammography to physical examination screening, which explains its lack of effect on breast cancer mortality.

One reason to doubt overdiagnosis in the context of our trial, is the “catch-up” of invasive breast cancers that occurred in the physical-examination-alone group with continued follow-up. However, after screening ceased in the trial in 1988, most women had access to provincial breast screening programs. It is likely that the majority of our participants, having been sensitized to a possible benefit of breast screening, volunteered for these programs. All of the programs include mammography; thus, the opportunity for overdiagnosis continued for women in both arms of the trial. Therefore, the apparent equivalence of cancers at the end of follow-up does not exclude overdiagnosis as an explanation for many of our findings.

Although we agree with Narod that researchers should seek an explanation for our results, we fear that this will not be possible unless they accept the recent proposal that a trial should be initiated comparing screening by use of mammography alone with screening by breast physical examination (6). We urge any researcher interested in such a trial to contact A. B. Miller directly; he will be happy to share a protocol that has been drafted for such a trial. Should such a trial not occur, we can only hope that new biomarkers will eventually result in more effective early detection or that new treatments for breast cancer will be so effective as to make breast screening unnecessary.

Anthony B. MillerCornelia J. BainesClaus Wall

REFERENCES


NOTES

Affiliations of authors: A. B. Miller, Abteilung Klinische Epidemiologie, Deutsches Krebsforschungszentrum, Heidelberg, Germany; C. J. Baines, Department of Public Health Sciences, University of Toronto, Ontario, Canada; C. Wall, Institute for Clinical Evaluative Sciences in Ontario, Toronto.

Correspondence to: Anthony B. Miller, M.B., FRCP, Abteilung Klinische Epidemiologie, Deutsches Krebsforschungszentrum, Postfach 101949, D69009 Heidelberg, Germany (e-mail: a.miller@dkfz.de).