Response to: “Beyond the mammography debate: a moderate perspective”

The Editor
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In his editorial and perspective, Dr. Constantine Kaniklidis covers a lot of ground, and there is much to agree with. Certainly, we should be moving forward to find and evaluate better ways of detecting, characterizing, and treating breast (and other types of) cancer. In fact, I lead a large program at the Ontario Institute for Cancer Research focused on exactly those goals.

But I must respectfully take issue with some of his statements. For example, he contends that “Only sufficiently powered randomized trials—if still feasible in this age ... can hope to be more decisive on the central issues of a debate". Here, the “debate” is about the value of mammography screening for breast cancer.

From a scientific point of view, the debate should be over. For example, an editorial in The Lancet summarizing the report of the Independent UK Panel on Breast Cancer Screening, led by Professor Sir Michael Marmot, stated that “The Panel's report, the latest and best available systematic review, shows that the UK breast-screening programme extends lives and that, overall, the benefits outweigh the harms.... Women need to have full and complete access to this latest evidence in order to make an informed choice about breast cancer screening". With few exceptions (Peter Gotzsche, Anthony Miller), scientists agree that mammography screening combined with expeditious appropriate therapy contributes to a mortality reduction of between 15% and 50%. Only this month, the International Agency for Research on Cancer (part of the World Health Organization) reported on the finding of its Working Group on Breast Cancer Screening that there was “sufficient evidence” that mammography screening reduces breast cancer mortality in women 50–74 years of age and “limited evidence” that mortality reduction in those 40–44 and 45–49. The report remarked that, for the 45–49 year age group, “the vote was almost evenly divided between ‘limited’ and ‘sufficient’ evidence”.

It is also agreed that mammography screening has limitations: some cancers are missed, and some women (3%–12%) will be recalled for additional noninvasive imaging and, in some cases, biopsy. Most of those women will not have breast cancer, but the additional procedures are performed as part of the process of ruling out the possibility of breast cancer, allowing for the earlier detection of 3–5 cancers per 1000 women and for approximately 1000 breast cancer deaths to be averted in Canada each year. Randomized trials can yield only part of the answer, typically providing evidence of efficacy, not effectiveness, in that they are carried out in the artificial “test tube” of a clinical trial, rather than in the real world. Additionally, they are normally analyzed according to the intention-to-treat principle—that is, the outcome for a participant is treated according to the allocation received (study or control), and not according to whether the intervention was actually received. For evidence of effectiveness, scientists are now looking to observational studies of actual-service screening programs whose data are analyzed both according to invitation to the intervention and actually having been screened. But, in any case, it is highly doubtful, given the evidence from previous randomized controlled trials and observational studies, that women would be willing to be randomized to an unscreened arm.

Kaniklidis also comments that the patients and frontline providers of screening, in terms of their actions, appear to be paying little attention to the debate. Although I might normally find such inattention distressing, in this case it is probably a good thing, because the media, blindly following the lead of Gina Kolata of The New York Times have largely taken a one-sided viewpoint on the issue of screening: against. They are finely attuned and devote column space to the findings of any study, however weak, that appears to downgrade the value of screening, while ignoring the preponderance of studies that demonstrate positive results.

Kaniklidis’s perspective article also refers to the fact that some authors (usually those who do not themselves treat breast cancer patients) question the benefit of screening in the context of modern adjuvant therapy, given that the randomized trials showing efficacy for such therapy were conducted 30–40 years ago. No trials explicitly show that outcomes for cancers detected when they are at a more advanced stage or larger within a given stage are as good as those achieved when the cancer is found earlier through screening. On the other hand, several publications from current service-screening programs in the modern era (that is, in the presence of currently used therapies) show a mortality reduction associated with participation in screening, presumably through the combination of earlier detection and prompt, appropriate therapy. And in Canada, participants and
nonparticipants in screening alike have access to the same therapies. Kaniklidis supports that fact in his discussion of trial consistency, where he points out that analysis of several screening trials showed a reduction in breast cancer deaths, but not in non-breast-cancer deaths.

Let us now consider the concerns that I have expressed regarding a serious problem in randomization within Canadian National Breast Screening Study (CNBSS) and the alternative explanation that Dr. Steven Narod has offered. Narod provides a hypothetical and plausible explanation that the lead time provided by mammography could have resulted in some cancers being detected in the prevalence round in the mammography arm when they would otherwise have surfaced in later years. And indeed, that is the intention of screening (although the goal is to discover and treat the cancers early enough to avert death). But no direct evidence touches on how many of those cancers detected earlier through screening resulted in breast cancer deaths. Narod’s estimate of the number of those cancers depends on assumptions about the lead time provided by screening in the CNBSS and on the amount of overdetection. Estimation of overdetection is challenging. An estimate of overdetection from a randomized controlled trial depends on correction for lead time and on an accurate knowledge of the pattern of screening of women in both arms after the imaging episodes in the trial. Nothing in the 2014 report of the CNBSS suggests that such adjustments could be applied with any accuracy.

On the other hand, as initially pointed out by Boyd et al., 17 of the 19 poor-prognosis cancers detected in the prevalence round in the mammography arm of the CNBSS were palpable, and only 5 such cancers appeared in the control arm. I note that clinical examination by palpation was performed immediately before women were registered into the open-book randomization used in the study. Those cancers represented a high probability for lethality. There is no need to make any assumptions or corrections to the data. The evidence is presented by Miller et al. in their 2014 publication. The exclusion of the deaths from those prevalent cancers shifts the hazard ratio by 19 percentage points from 1.09 (mammography screening increases mortality) to 0.9 (screening reduces mortality)! Although those estimates are statistically nonsignificant, it seems to have been dangerous to be assigned to the mammography arm of CNBSS1, especially in the prevalence screening round, in which women were 46% more likely to die of breast cancer.

Kaniklidis remarks that, in many of the trials, attention was given mainly to quantification of the benefit; the limitations or harms (women recalled who were found not to have breast cancer, those who had negative biopsies, and overdetection) were not quantified—an excellent point. I don’t think that many were aware of the concept of overdetection at the time of the randomized controlled trials. It is entirely appropriate that consideration be given to the benefits, limitations, and harms, but those factors are meaningful only if they can be weighed on a common scale. Otherwise, how does a recall for ultrasonography examination after a suspicious screen compare with a year (or ten years) of life saved? Health economists use the QALY—quality-adjusted life-year—as a measure for comparing such disparate variables, but weightings must still be established: By what factor is quality of life reduced by the experience of a screening recall or a negative biopsy? Research in this area is still needed.

The Kaniklidis editorial suggests that guideline panels with a radiologist member do not make recommendations against routine screening. There is a suggestion that this phenomenon is self-serving, and perhaps to some extent, it is. But another way of looking at it is that the groups who have made recommendations against mammography screening usually lack input from radiologists or others who are knowledgeable about cancer imaging. Given such input, and given the evidence supporting benefit, a committee would be unlikely to recommend against screening. I sense that those who create task forces on guidelines believe that, like “blind Justice,” it is better for those making recommendations about an intervention to have minimal expertise in the area. I agree with Kaniklidis that what is needed is a combination of balance and expertise in the composition of such groups. The presence of individuals with expertise in medical imaging on the Task Force would have prevented the confusion that occurred in the 2009 U.S. Preventive Services Task Force recommendations. There, the panel inadvertently quoted the number of women required to be invited to participate in a randomized trial to prevent 1 breast cancer death rather than the appropriate metric, the number of women actually needed to be screened—a number smaller by more than a factor of 3!

Returning to the idea of moving forward, I wholeheartedly agree. It is absolutely imperative to set our energies to finding biomarkers that will allow for better characterization of the disease and for avoidance of overdiagnosis and overtreatment. In fact, a detection tool better than mammography for screening—possibly a circulating marker—has to be found. Revising screening guidelines to reduce the detection of so-called IN-S [indolent lesions of epithelial origin] would make sense only if it can be done without increasing the risk of missing detection of a potentially lethal breast cancer. It probably would be better to develop more informative lab tests to avoid overtreating IN-S. As Narod recently wrote regarding ductal carcinoma in situ, undertreatment engenders a risk of recurrence, suggesting that “women with [ductal carcinoma in situ] should be offered the same treatment options as women with small palpable stage I breast cancers”.

But, while that work goes forward, if the argument over mammography screening—for which we have an abundance of experience and good data on an intervention that has already been implemented and is working to reduce mortality—is not first clearly resolved, how will we deal with the murkier and more complex issues around biomarkers? I am concerned that we will just get bogged down in the same sorts of issues. And in the meantime, we may lose the opportunity we have right now to save hundreds of thousands of women’s lives.

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CONFLICT OF INTEREST DISCLOSURES
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REFERENCES