

Get the Facts Straight

TO THE EDITOR: The article by Demicheli et al¹ concludes that premenopausal women should not be screened for breast cancer because they contend that the earlier treatment of breast cancers among these women hastens their demise. It would seem that the authors have a hypothesis that they wish to prove, and that they have misunderstood the facts, thinking that they fit the hypothesis. Peer review should have picked up the important, factually incorrect statements that seem to lend support to their hypothesis. Since their argument is based on factually incorrect information, and this could result in the unnecessary loss of life, the authors should provide corrections.

Contrary to their assertions, the randomized controlled trials of mammography screening do not “all” show an early mortality excess for younger women. As with any such trials, the results in the early years reveal very small numbers. There is clearly statistical fluctuation that is to be expected since, even in the absence of screening, women are not expected to die from breast cancer at exactly the same time in the two groups of a trial. If these small numbers had any validity, then large trials would never be necessary. One need only look at the graphs of the survival data from the Malmö I trial² and the Gothenberg trial,³ as well as the combined Swedish data⁴ to see this effect. The curves weave back and forth in the early years of follow-up, consistent with statistical fluctuation. Malmö II shows a clear benefit from the beginning for “younger” women.² It has also been suggested that some deaths among the control group that were not counted may have been due to undiagnosed breast cancer. The authors also failed to take into account the fact that deaths among women in the screened group may also include women who refused, and were never screened. The analysis by Cox that is cited represents an artifact of incomplete analysis. Any adjustment for multiple testing would render the observation nonsignificant.

The article provides two other importantly incorrect statements. There are, indeed, animal studies suggesting that, for some cancers, following the removal of the primary lesion, the growth rate of metastatic lesions does increase. What the authors neglected to point out is that this effect is transient, lasting for a few hours to, at most, a few days. They provide additional misleading information by suggesting that this results in earlier death. With the possible exception of their reference 15 from 1979, the other laboratory studies specifically state that this phenomenon did not lead to earlier deaths.

Their own survival curves fail to show any earlier mortality among the premenopausal women. They do not provide

sufficient data to permit an independent understanding of their analysis. None of their observations are statistically significant, with the exception of the women with very large cancers (generally not seen in screening programs). In fact, the survival curves suggest that there is no difference in survival for women with T1 lesions, and that the younger women have better survival, early on, for T2 and T3 cancers (contradicting their own interpretation). Furthermore, since their data come from the prescreening era, there were likely few of the T1a and T1b lesions that are now found by screening.

Contrary to their contention, there is no scientific evidence that screening women younger than 50 years (or premenopausal women) leads to an excess of early breast cancer deaths. To the contrary, the randomized, controlled trials have demonstrated a benefit for women ages 40 to 49 years, and this has been confirmed in large studies of service screening in Sweden.^{5,6}

Finally, since women in the screening trials who were allocated to screening and refused are still counted in the analyses as having been screened, the authors have no way of knowing whether the deaths in the screened groups (with the exception of the Canadian trial of volunteers) were among women who actually were screened.

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The author indicated no potential conflicts of interest.

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Delayed Benefit of Mammography Screening in Premenopausal Women

TO THE EDITOR: Demicheli et al point out that in the mammography screening trials, an early excess in breast cancer mortality is seen among premenopausal women who undergo screening.¹ Yet a reduction in breast cancer mortality in the screened group is evident much later (after approximately 12 years).² The authors suggest that surgery may perturb the natural history of breast cancer (perhaps by releasing cytokines that could bestow autonomy on micrometastases), and that the early excess in mortality among premenopausal women who undergo mammography screening might be attributed to surgery (early detection of breast cancer results in early surgery, and this in turn produces an early excess in mortality).

However, the authors fail to provide an explanation for the apparent long-term benefit of mammography screening in premenopausal women. We suggest that surgical perturbation of the natural history of breast cancer might explain this observation. At the conclusion of the mammography screening trials, women in the control (unscreened) groups were often invited to undergo screening.³ As a result, an excess of cancers were diagnosed and treated surgically in the control groups following completion of the screening trials. If surgery does indeed perturb the natural history of breast cancer, then inviting the controls to undergo delayed screening may have resulted in a delayed increase in breast cancer mortality in those women. Thus long-term comparisons of breast cancer mortality trends between control and study groups may give the false impression that screening has a delayed benefit in the study groups, when, in fact, the better long-term outcome of women in the study groups might actually be due to a delayed one-time increase in breast cancer mortality in the controls.

Demicheli et al suggest that the potential effects of surgery might differ between pre- and postmenopausal women. If so, then the hormonal milieu at the time of surgery may influence early breast cancer mortality. Several retrospective studies have suggested that this is indeed the case, and that the timing of surgery in relation to the menstrual cycle may have an impact.⁴ Clearly, randomized prospective trials are needed to resolve these issues. Neoadjuvant hormonal therapy may ultimately prove effective in modulating these effects.

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IN REPLY: Dr Daniel B. Kopans harshly criticizes our article.¹ We thank him for giving us the opportunity to rediscuss some points of our report. We will address his questions point by point.

First, we wish to point out that Dr Kopans attributes to us a statement (“the article. . .concludes that premenopausal women should not be screened for breast cancer. . .”) that was not part of our conclusions because it does not correspond to our interpretation of the results. Even the point regarding the “hypothesis that [we] wish to prove” is not pertinent to our article. We are well aware that it is virtually impossible to prove that a given model is true, and that models can only be disproved (when they result in significant departure from observed findings). Our article simply suggests a possible biology-based explanation of clinical observations, and no statement about “proven hypotheses” is reported.

Dr Kopans denies the occurrence of an early mortality excess for younger women. The question of early mortality excess has recently been addressed by C.J. Baines.^{2,3} We wish to note here that the denied occurrence of this phenomenon in the Malmo trial that Dr Kopans takes as an example is explicitly reported by its principal investigator I. Andersson⁴; one needs to read the papers in addition to looking at a few graphs. Moreover, Dr Kopans states that the analysis of Cox “represents an artifact” and that “any adjustment for multiple testing would render the observation nonsignificant”—an occurrence that should be verified, however, and not assumed a priori. We are aware of the complexity of planning, carrying out, and analyzing randomized controlled trials on mammographic screening. The resulting difficulty of achieving unquestionable results is witnessed by the well-known controversy about screening effectiveness. We do not have a fideistic attitude toward the *P* value from either univariate or multivariate analysis and we believe that early mortality excess of invited women, documented consistently across screening trials, countries, and time, may maintain its clinical and scientific significance even in the absence of statistical significance.

Animal studies about the role of primary tumor removal may be performed either on macrometastases or on micrometastases, two very different experimental systems. Dr Kopans, when pointing out the “transient” surgery effect, refers to animal models in which experimental

macroscopic “metastases” (mainly subcutaneous implants smaller than the “primary”) were studied. Most of these investigations are focused on local surgery-induced changes and do not report data on animal survival. They prove the proliferation increase, which we consider to be one of the possible mechanisms of metastatic development acceleration, while they little say about its role in the natural history of the neoplastic disease. Dr Kopans’ criticism completely ignores angiogenesis induction by primary tumor removal—a further important acceleration mechanism⁵ observed only in animal studies on micrometastases. Studies on micrometastases that are much more similar to the clinical setting prove that noncurative primary tumor removal may produce proliferation enhancement or angiogenesis triggering, thus resulting in tumor dormancy interruption and in prognosis worsening.^{6,7} In particular, a biphasic effect of surgery on life span was observed in a specific animal model⁶ in which very early surgery resulted in a few long-term survivors, while more delayed surgery displayed a detrimental effect on life span. Another example comes from studies on the fertility cycle influence on surgery effectiveness for mammary carcinoma in mice: the same surgical maneuver results in different outcomes when performed in different times within the estrous cycle.⁸ Therefore, Dr Kopans is wrong in underestimating the importance of “transient” phenomena that can throw a switch, with life-long implications. Can he declare that similar phenomena do not occur in humans and that both favorable and detrimental effects cannot result from primary tumor removal? Metastatic growth enhancement, tumor dormancy, and modulation of host-tumor interactions, which are the main features of the metastasis development model we are proposing, are well known to “oncologists of mice,” and we believe that these concepts, *mutatis mutandis*, may be relevant for humans and should be taken into account even by clinical oncologists without blinders.

Another point of Dr Kopans is about what may be noticed in our survival curves. He compares the survival rates of pre- and postmenopausal patients within the categories of tumor size, instead of comparing survival changes when tumor size drops from more than to less than 2 cm in diameter within the same menopausal status. This “look at the graphs” approach does not allow him to perceive that premenopausal patients obtain less improvement by primary tumor undersizing than their postmenopausal counterparts, thus suggesting a possible reason for the diminished effect of screening for the former.

For the last point, because of lead-time bias, length bias, and class bias, it is widely accepted that only comparisons between populations randomly allocated to be invited and not to be invited to screening may provide meaningful data. Obviously, if each invited woman had actually been screened and all noninvited women did not undergo mammography, we could compare “screened” versus “not

screened” instead of “invited” versus “not invited.” The compliance, which in Scandinavian trials was near 80%, is a useful measure of how near to identical the invited were to the screened group. Therefore, Dr Kopans, who is certainly aware of the trap of using surrogate end points, should be reassured about the comparability between arms. We cannot believe that Dr Kopans assumes that, *ceteris paribus*, throwing the invitation letter into the wastepaper basket is meaningfully different from not receiving the invitation.

Jatoi et al suggest another possible and, in our opinion, probable effect of surgical primary tumor removal on the pattern of mortality in screening trials. According to our hypothesis, women in the control arm will show a mortality increase following invitation to undergo delayed screening, resulting in a trend toward mortality curves opening wide. It should be noted, however, that this phenomenon is temporary, as well as that involving invited women in the early years,¹⁰ and should not affect the long lasting results of the trial. These considerations add further elements to the complexity of understanding results from screening trials.

Regarding the considerations about the timing of surgery in relation to the menstrual cycle, we agree with Jatoi. Since the early report,¹⁰ data supporting this point have been produced,^{11,12} and we hope that the often-solicited randomized prospective clinical trial on this issue will be at last carried out and will definitively answer the question.

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