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The Mammographic Screening Trials: Commentary on the Recent Work by Olsen and Gøtzsche

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Since the publication of the results of the Greater New York Trial and the Swedish Two-County Trial in the 1970s and 1980s, there has been a general consensus that screening for breast cancer with mammography reduces mortality from the disease. The results of these pioneering trials for the most part have been subsequently confirmed by later trials in Sweden, Canada, and the United Kingdom. Although some issues endure, most notably those regarding cost-effectiveness of screening in particular age groups, as well as concerns about harms associated with false positive results, the evidence that screening reduces deaths from breast cancer has steadily increased, and the consensus regarding the benefit of screening has grown stronger.

The evidence that screening with mammography is associated with a lower breast cancer death rate recently was challenged when *The Lancet* published a research letter by Olsen and Gøtzsche[1] (OG) describing their overview of the mammographic screening trials. OG asserted that "…the reliable evidence does not indicate any survival benefit of mass screening for breast cancer," and they maintained that screening leads to more aggressive treatment; thus, screening is not only without benefit, but in addition to representing a waste of health resources, it actually results in net harms.

This article has generated considerable print and electronic media attention, with a spectrum of opinions ranging from complete support for the conclusions of OG to complete dissent. Yet, despite the public exchange, the OG report has failed to convince institutional leaders in the United Kingdom, Sweden, the Netherlands, or the United States to change screening policy. Most have publicly reaffirmed the current recommendations supporting regular mammography. Having thoroughly considered all available information, including the OG report, the US Preventive Services Task Force retained its current recommendation that women have regular mammograms every one to two years, and in fact, expanded the recommendation to include women in their forties. In addition, 10 leading medical organizations published a full-page open letter in the *New York Times* on January 31, 2002, supporting the value of early breast cancer detection.†

In our opinion, which is based on evidence accrued over decades of scientific research on breast cancer screening, and countless, independent expert peer reviews of the study designs, data, and conclusions of the trials, the scientific foundation for the value of early breast cancer detection with mammography is sound. To see why, consider Figure 1, which summarizes the most recently published results of the mammographic screening trials. The results indicate that there is a statistically significant 24% reduction in breast cancer mortality associated with an invitation to screening. The distinction between "invited to screening" versus "screened" becomes clear when you consider that a randomized trial of screening examines mortality rates in the study arm offered screening versus the study arm offered usual care.

†The following organizations co-signed the open letter message: American Academy of Family Physicians; American Cancer Society; American College of Obstetricians and Gynecologists; American College of Physicians—American Society of Internal Medicine; American College of Preventive Medicine; American Medical Association; Cancer Research Foundation of America; National Medical Association; Oncology Nursing Society; and Society of Gynecologic Oncologists.

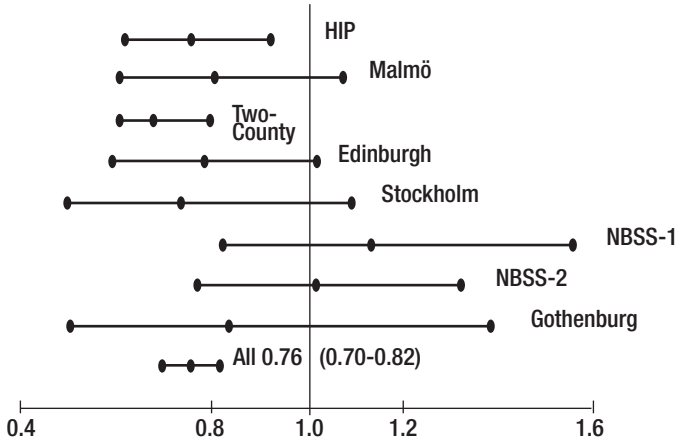
While this underlying methodology underestimates the benefit of screening (since some deaths from breast cancer occurred in women in the invited group that did not get screened, and some deaths from breast cancer were avoided in control-group women who sought mammography on their own), comparing breast cancer death rates according to the initial randomization eliminates the effect of selection bias.

The data in these trials have undergone repeated independent scrutiny by individuals, and also under the auspices of leading medical and scientific organizations, including an audit and reanalysis of the individual data from the five Swedish trials.[2,3] The Swedish overview involved a complete review of all patient records by an independent panel of breast cancer experts who were unaware of whether or not patients were in the study group (invited to screening) or in the control group. OG and Horton have called for such a reanalysis as the only solution to this controversy, apparently overlooking or ignoring that it had already been done and published in *The Lancet* in 1993.[1,4] More recent evidence from observational studies indicates that in organized service screening programs, the benefit is greater than that observed in the trials.[5] A recent study by Tabár, et al., found that providing screening to a population of Swedish women in two counties was associated with an overall 50% breast cancer mortality reduction in that population.[5] Moreover, among women who actually received screening, the mortality reduction was 63 percent.

In view of the history of supporting scientific evidence, how do OG come to such different and startling conclusions? The problem lies in their dual strategy of 1) excluding five of seven trials from their analysis (all but the Malmö and Canadian trials) on the basis of alleged methodological inferiority, and 2) their use of all-cause mortality rather than breast cancer mortality as the end point. Their criteria for these methodological choices are

FIGURE **1**

Relative Rate of Breast Cancer Death in the Eight Randomized Trials of Breast Cancer Screening



specified in a longer document available from the Internet (image.thelancet.com/lancet/extra/fullreport.pdf). In this online document, it is evident that the classification of both study and end point quality is based on subjective judgments as well as misinterpretation of the individual trial methodology. In our opinion, there are numerous fundamental flaws in the judgments, and thus the conclusions of OG. We provide some examples below:

1. OG rejected five of seven trials from inclusion in their meta-analysis because of alleged methodological flaws. Each of the excluded studies showed a mortality reduction associated with an invitation to mammographic screening. However, there is little evidence that the alleged flaws were either real or even meaningful in affecting the study results. Indeed, many of their complaints represent a failure to carefully examine early trial publications. For example, accusations of lack of proper randomization in the Swedish Two-County Trial can be seen to be unfounded from some of the earliest publications.[6] In addition, allegations of inconsistency over time in reporting in the Two-County Trial pertain to honest and detailed reporting by the trialists of differences between classification of cause of

death by the original trial end point committee and an independent overview committee. These differences did not alter the results or conclusions of the individual Swedish trials. This explanation and the impact of reclassification were highlighted in literature[2] cited by the OG report, yet these details go unmentioned in their report.

2. OG judged that the Health Insurance Plan (HIP) of Greater New York study's cause of death classification was unreliable because in the blinded review (i.e., reviewers did not know whether the death was in the study group or the control group) there were fewer breast cancer deaths in the study group than in the control group. The plausible alternative explanation, rejected by OG, is that this difference is due to the effectiveness of the intervention; i.e., breast cancer screening reduces deaths from breast cancer.

3. OG's report contains arithmetic inconsistencies. For example the total numbers of all-cause deaths at seven years that they report for the Two-County study are smaller than the numbers reported for the age subgroup 50+. The age range of the Malmö study was misquoted, and the numbers reported for the age subgroups in the Stockholm trial do not sum to give the totals in all ages.

4. Perhaps one of the most contentious issues is the claim by OG that only a reduction in all-cause mortality (not breast cancer mortality) would indicate a benefit from mammography screening. This position is based on an alleged higher rate of non-breast cancer deaths among the breast cancer cases in the group invited to screening compared with the control group in the randomized trials. Setting aside the fact that breast cancer screening can't be expected to save lives from hip fractures and diabetes, there are other flaws with their argument, including their assessment of this difference. The most important is that the authors failed to take lead-time into account in their calculations. If breast cancer is diagnosed, on average, three years earlier as the result of screening, then study women with breast cancer detected by mammography are, on average, classified as breast cancer "cases" three years earlier than control-group women whose cancers are detected by other means. Because of this lead-time, and thus faster accumulation of breast cancer cases in the study group, during the follow-up period there is an average of three more years for the screen-detected breast cancer patients to die from other causes, and thus be classified as a non-breast cancer death. While this gives the appearance of a higher rate of all-cause mortality in these breast cancer cases, statistical adjustment for the additional follow-up time in the study group, reveals that in fact all-cause mortality in the study group cases is lower. Taking account of this fact, it was shown in 1989 that there was no evidence of bias in classification of cause of death, and no compensatory increase in deaths from other causes in the group invited to screening.[7] Also, in 1996, an excess mortality analysis was carried out with the Swedish overview data, avoiding the classification of cause of death which OG distrust, and the results confirmed the mortality reduction.[3] It is also worth noting that more than 90 percent of all-cause mortality cannot be affected by this intervention. Therefore a trial with more than a million subjects would be required to detect a statistically significant reduction in all-cause mortality. Again, while OG cite this paper in their review, they do not discuss its relevance to dismissing their concern regarding the non-cancer mortality rates.

5. Finally, OG's remarks on the cardiovascular complications of radiotherapy apply to techniques of radiotherapy much less sophisticated than those in current use.[8] They also assert that screening leads to more aggressive surgery. This conclusion is belied by the fact that the epoch of mammography has led to a substantial move away from mastectomy toward breast conserving surgery.[9]

Because of serious flaws such as those noted

above, we conclude that OG's review provides no grounds for the medical community to alter the conclusion that has been based on millions of person-years of experimental evidence, i.e., that breast cancer screening leads to a substantial reduction in mortality from the disease. Health care professionals should have confidence that more meticulous and credible reviews have been carried out by numerous independent expert panels in Europe and the United States and consistently reached the same conclusion: early breast cancer detection and treatment results in decreased breast cancer mortality. Clinicians should have confidence in the current recommendations issued by leading organizations, and they should impart that confidence to their patients. We should remain vigilant to avoid any setbacks to the progress we've made in encouraging women to get regular mammograms.

Women who have developed confidence in breast cancer screening should not be intimidated, and overworked staff who go to great lengths to make screening work should not have their morale damaged by poor quality reviews such as that of OG. It would be wrong to use this error-prone analysis to discourage an early detection procedure that has been shown in trial after trial to reduce breast cancer mortality.

As we noted in the beginning of this editorial, over the years there have been issues related to breast cancer screening for which it has been entirely reasonable for experts to disagree. Because breast cancer is a leading chronic condition affecting women, and one of women's leading health concerns, these issues and controversies acquire easy visibility. As is often the case in highly visible medical issues, when the underlying scientific evidence for a practice is challenged and dismissed with great confidence, authority, and little detail, supporters of the practice are left to counter with scientific refutations that may seem arcane, complex, and defensive. However, such refutations are essential to the resolution of important medical and public health issues. For this reason, undoubtedly there will continue to be an accumulation of evidence-based refutation of the OG article in the coming months to add to that already in print.[10,11,12]

REFERENCES

1. Olsen O, Gøtzsche PC. Cochrane review on screening for breast cancer with mammography. Lancet 2001;358:1340-1342.

2. Nyström L, Larsson LG. Breast cancer screening with mammography. Lancet 1993;341:1531-1532.

3. Larsson LG, Nyström L, Wall S, et al. The Swedish randomised mammography screening trials: Analysis of their effect on the breast cancer related excess mortality. J Med Screen 1996;3:129-132.

4. Horton R. Screening mammography: An overview revisited. Lancet 2001;358:1284-1285.

5. Tabár L, Vitak B, Chen HH, et al. Beyond randomized controlled trials: Organized mammographic screening substantially reduces breast carcinoma mortality. Cancer 2001;91:1724-1731.

6. Tabár L, Gad A. Screening for breast cancer: The Swedish Trial. Radiology 1981;138:219-222.

7. Tabár L, Fagerberg G, Duffy SW, et al. The Swedish Two-County Trial of mammographic screening for breast cancer: Recent results and calculation of benefit. J Epidemiol Community Health 1989;43:107-114.

8. Overgaard J, Bartelink H. Breast cancer survival advantage with radiotherapy. Lancet 2000; 356:1269-1270.

9. Wingo PA, Guest JL, McGinnis L, et al. Patterns of inpatient surgeries for the top four cancers in the United States, National Hospital Discharge Survey, 1988-1995. Cancer Causes Control 2000;11:497-512.

10. Wald N. Populist instead of professional. J Med Screen 2000;7:1.

11. de Koning HJ. Assessment of nationwide cancer-screening programmes. Lancet 2000;355: 80-81.

12. Duffy SW. Interpretation of the breast screening trials: A commentary on the recent paper by Gøtzsche and Olsen. The Breast 2001;20: 209-212.