COMMENTARIES

Mammography Screening: Are Women Really Giving Informed Consent?

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Many women remain unaware of the extent to which efforts to achieve breast cancer control through mammography screening may be doing harm as well as good. An unacknowledged harm is that for up to 11 years after the initiation of breast cancer screening in women aged 40–49 years, screened women face a higher death rate from breast cancer than unscreened control women, although that is contrary to what one would expect *(1).*

The belief in early detection as a universal good is widespread among women, health care professionals, and the media, all of whom focus on the benefits from mammography screening. Although the bad news about excess breast cancer deaths was published in the Journal *(1),* in 6 years it has been cited only eight times, four of which were by the same research group. Discussing the bad news is considered unethical and alarmist. Recently, the U.S. Preventive Services Task Force ignored the issue *(2);* in contrast, the International Agency for Research on Cancer acknowledged it *(3).* The truth about mammography may be that early detection is often but not always beneficial for women who are screened. The truth may be that early adverse outcomes for some premenopausal women *(4)* are only later counterbalanced by beneficial outcomes for others in the age group 40–49 years. Table 1 presents an overview of the results from the two Canadian trials *(5,6)* and the recent meta-analysis of five Swedish trials *(7).* The meta-analysis, a response to earlier criticism *(8),* presents the best available analysis of the Swedish screening trials. The Edinburgh trial is excluded from Table 1 because of problems with randomization *(2).* With the exception of results for women aged 60–69 years, Table 1 reveals that the reduction in deaths from breast cancer achieved by screening is modest. Because the rate ratios are reported after extended follow-up, the mortality paradox is not apparent in the table.

Nevertheless, the mortality paradox in women aged 40–49 years 3–10 years after screening is initiated—that is, an increased number of deaths from breast cancer in the groups invited to screening instead of the expected reduction in deaths—has been documented consistently across screening trials, countries, and time *(9–12).* Fig. 1, which is based on a meta-analysis of randomized screening trials, shows both the initial higher rate of deaths from breast cancer in screened women than in unscreened control women and the crossover point at 11 years, when the reduction in mortality begins to occur in screened women relative to unscreened control women *(1).* Should this paradox be ignored because, overall, the difference is not statistically significant?

Women are supposed to be informed before making decisions about screening, but unfortunately, most are ill-informed about both the hazards and the benefits of screening *(13,14).* Shouldn't women aged 40–49 years know that, 3 years after screening starts, their chance of death from breast cancer is more than double that for unscreened control women *(1)*? Shouldn't they be informed that it will take 16 years after they start screening to reduce their chance of death from breast cancer by a mere 9% *(7)*? Ironically, the twofold increased risk of death from breast cancer in the third year after initiating screening is statistically significant (rate ratio = 2.4, 95% confidence interval = 1.1 to 5.4) but has been dismissed as chance, whereas the 9% decreased risk of death from breast cancer 16 years after initiating screening is statistically insignificant but fuels enthusiasm for screening *(7).*

In 1985, the first report of the Swedish Two-County Trial clearly demonstrated the breast cancer mortality paradox in women aged 40–49 years *(12).* A relative risk for breast cancer death of 1.26 (95% confidence interval = 0.56 to 2.84), that is, a 26% excess of breast cancer deaths was found for women who were invited to be screened versus unscreened control women, at 7-year follow-up from initiation of screening. A similar increased risk of breast cancer death in screened women was already being observed in the Canadian National Breast Screening Study, which had begun in 1980. It was very disturbing.

In 1992, 7-year results from the Canadian trial for women aged 40–49 years revealed 36% more deaths from breast cancer among screened women than among unscreened women *(15).* At the 10-year follow-up, this percentage decreased to 14% *(16).* Neither result was statistically significant. Although similar trends were observed in other screening trials *(9–12),* condemnation of the Canadian trial because of the increased number of breast cancer deaths in screened women compared with unscreened control women was widespread, most colorfully expressed in the following quote in *Science (17):* "Now hold it, we're not going out and killing women. This demands an explanation." Surprisingly, the quote came from one who had reported the same mortality paradox in the 1980s and 1990s *(12,18).* The statement was wrong inasmuch as it attributed the mortality paradox uniquely to the Canadian study, but it was absolutely correct in that no one offering screening to women wanted to "kill" them. Furthermore, an explanation for the paradox is certainly long overdue.

Persuasive rationales have been presented to the public that mammography screening is effective. One argument says that because modern mammography outperforms mammography done 20 years ago, it will be more effective in reducing the number of deaths from breast cancer than the mammography in

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See "Note" following "References."

DOI: 10.1093/jnci/djg026

Table 1. Overview of Swedish and Canadian screening trials: rate ratios for risk of breast cancer death

Study/mean follow-up time, y	Age group, y	Rate ratio* (95% CI)
CNBSS-1† *(5)*/13	40–49	0.97 (0.74 to 1.27)
CNBSS-2 *(6)*/13	50–59	1.02 (0.78 to 1.33)
Swedish meta-analysis‡ *(7)*/15.8	40–49	0.91 (0.76 to 1.09)
	50–59	0.88 (0.75 to 1.03)
	60–69	0.73 (0.61 to 0.87)

*Follow-up model. CI = confidence interval.
†CNBSS = Canadian National Breast Screening Study.
‡Malmö Trials 1 and 2, Östergötland, Stockholm, and Göteborg.

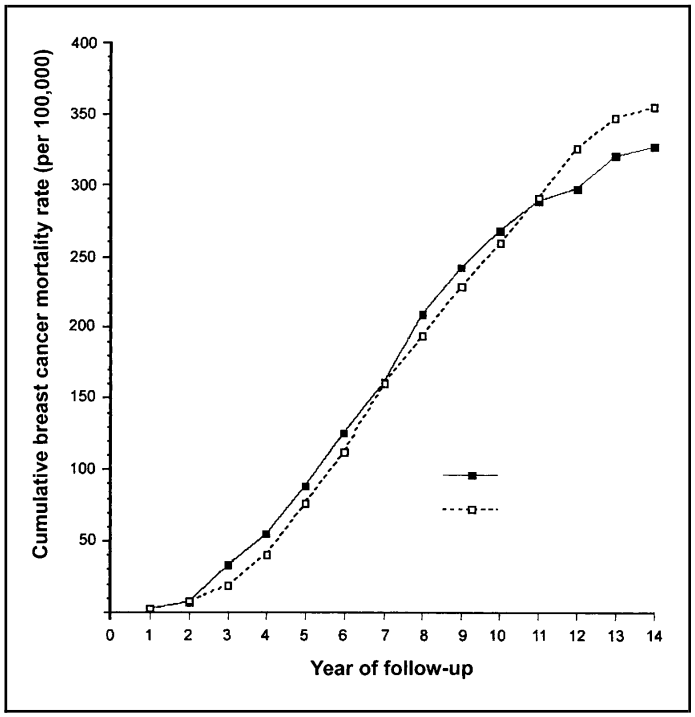

Fig. 1. Overall cumulative breast cancer mortality rates per 100 000 women aged 40–49 years in intervention and control groups from seven trials of breast screening. At 10 years of follow-up from the first screening with over 800 000 person-years of experience in each group, breast cancer mortality was not statistically significantly reduced in women who were screened. Reproduced with permission *(1)*.

the screening trials. Yet, in 2000, cancer detection rates at first screening (5.9 breast cancers per 1000 women screened) using modern mammography in combination with clinical breast examination in a Canadian population–screening program for women aged 50–59 years were lower than those achieved in the l980s with the same two modalities in the Canadian trial (7.2 breast cancers per 1000 women screened) *(19,20)*. Recent investigative journalism has described alarming inadequacies in community-screening mammography in the United States *(21)*. Obviously, modern mammography does not necessarily deliver what is promised.

Another approach is to combine trial and population data and report major reductions in breast cancer mortality which far exceed those observed in randomized controlled trials. In 2001, based on data from two Swedish counties, a 63% reduction in breast cancer deaths was reported for women aged 40–69 years who accepted screening (i.e., compliant women) compared with unscreened women. This analysis compared three time periods: 1968–1977, 1978–1987, and 1988–1996 *(22)*. In 2002, the same authors, analyzing data from seven Swedish counties again with a before/after design, reported a 44% reduction in the number of breast cancer deaths in compliant women aged 40–69 years *(23)*. Finally in 2003, another iteration involving the two Swedish counties (1958–1977 versus 1978–1997) showed a 44% reduction in breast cancer deaths in compliant women aged 40–69 years, but this time an estimate was also given for women aged 40–49 years, namely, a reduction of 48% *(24)*. All three before/after comparisons required complex statistical maneuvers to overcome the bias inherent in such studies. Those who favor this second approach over the "gold standard" of randomized controlled studies may infer that women who do not accept an invitation to be screened have some characteristic that explains the breast cancer mortality paradox in screening trials. The mantra after all is "mammography saves lives," and the substantial mortality reductions observed in these before/after studies support the mantra.

However, both the inference and the mantra may be wrong. The mortality paradox is unlikely to be explained by noncompliance with screening. Unlike any other trial, the Canadian trial had virtually 100% compliance with mammography screening at the first screen and about 90% compliance at subsequent screens *(15)*. Unlike other trials, the Canadian trial required that women aged 40–49 years be screened every 12 months *(15)* compared with every 18–33 months in the Swedish trials *(7)*. Clearly, more women who were assigned to screening actually received mammography in the Canadian trial than in other trials, and Canadian women also received it much more frequently than the Swedish women. In such circumstances, a logical inference is that any adverse consequences of mammography screening, even if found in only a subgroup of women, would be more likely to be seen in the Canadian trial. The mortality paradox is not the result of flawed randomization, imperfect mammography *(25)*, contamination of the control group *(5)*, or major flaws in or differences among trials. In fact, the Canadian and Swedish trial results are similar—a 3% decline in the number of deaths from breast cancer 13 years after the initiation of screening for Canadian women aged 40–49 years *(5)* and a 9% decline 16 years after the initiation of screening in the recent Swedish overview *(7)*; neither result was statistically significant. Moreover, the curve for the cumulative number of deaths from breast cancer in screened women crosses over the curve for the cumulative number of deaths in control women at similar times in different screening studies *(1)*. Fig. 1 shows the crossover occurring at 11 years. In the Canadian study, the 14% increase in breast cancer deaths in screened women versus unscreened control women at the 10-year follow-up declines to a 3% decrease in breast cancer deaths in screened women versus unscreened control women at the 13-year follow-up *(5)*. In the Two-County trial, the crossover had yet to occur at 11 years *(26)*.

In all trials, some women screened at age 40–49 years die prematurely of breast cancer when compared with unscreened control women. It is interesting that a recent computer simulation with data from the Milan National Cancer Institute *(27)* yielded an early peak in postsurgical breast cancer relapse at 18 months consistent with the increased risk of death from breast cancer at 3 years after the initiation of screening, as reported in the meta-analysis by Cox *(1)*.

In spite of the transience of the mortality paradox, it is imperative to investigate the underlying biologic mechanisms. Is it

possible that earlier detection in some women causes earlier death? How could this happen? Surgical removal of a primary breast tumor from premenopausal women with involved lymph nodes may trigger the growth of temporarily dormant micrometastases in 20% of the patients *(4),* which is consistent with earlier animal studies *(28).* Retsky et al. *(4)* speculate that patients with lymph node–negative breast cancer benefit from screening regardless of age or menopausal status, whereas premenopausal patients with lymph node–positive breast cancer do not. In the latter group of women, the same growth factors that promote wound healing after surgery could reasonably promote residual tumor growth. Dormant micrometastases can remain latent for long periods with the potential to grow or regress in response to systemic triggers *(29,30).* Thus, even breast cancer patients without involved lymph nodes may be disadvantaged by the consequences of surgical intervention in response to screening if they have distant dormant metastases. In 1980, Fisher *(31)* postulated that breast cancer may spread hematogenously before clinical or mammographic detection and that the eventual outcome would depend on tumor–host interactions. One of these interactions may be mediated by antiangiogenic factors *(32,33).* When tumors secrete such factors and inhibit angiogenesis in latent metastases, the removal of the primary tumor allows angiogenesis to stimulate the growth of micrometastases. If postsurgical activation of dormant metastases does indeed explain the higher rate of breast cancer mortality in the early years of screening women aged 40–49 years, neoadjuvant chemotherapy before surgery may prove useful in the future *(34).* Why all of these factors would not apply equally to women 50 years old and older is not clear, but the estrogenic milieu in younger women may be a factor.

Another biologic issue affecting younger women is the effect of radiation. If it is true that the low-energy x-rays used in screening mammography are more hazardous per unit dose than high-energy x-rays, as determined by oncogenic transformation and chromosomal aberration end points *(35),* younger women may be wise to defer mammography until age 45 or 50 years *(35).* At older ages, the magnitude of the benefit from screening mammography outweighs the doubling of radiation risk associated with low- versus high-energy x-rays *(35).*

A complete understanding of host–tumor interactions may be years away. But we already know enough to recognize that the breast cancer mortality paradox is not biologic nonsense. Whether it is truly a statistical artifact should be settled when results are published for the U.K. trial of mammography screening, which recruited women as they turned 40 years old, allowing a 10-year follow-up of women who remained in their 40s for the study period *(36).*

Fear has long goaded women to seek screening. The cumulative risk of developing breast cancer is one in nine (11%) in a woman's lifetime. This risk has led some young women to believe that 11% is their immediate risk of getting breast cancer. Women with an aunt diagnosed at age 75 years too often assume that they themselves are at increased risk of getting breast cancer long before they turn 50 years old. And too many women fail to realize that their risk of dying of breast cancer is much less than their risk of developing breast cancer. Women believe that 40% of all deaths in women are associated with breast cancer when the correct figure is closer to 4%. Women triumphantly announce they are "breast cancer survivors" if their breast cancers were diagnosed mammographically—last year! They are anything but well informed. They may not even want to be well informed. As one woman, a high-level American executive who wishes anonymity, wrote, "I'm terrified of breast cancer . . . . truthfully, I don't want quite this much information—or history—on this scary topic."

Women are frightened. Unfortunately, I may be causing even more fear. Yet surely it is preferable to confront fear that is based on available evidence rather than fear that is based on hyperbole. We live in an era in which lip service is paid to the concept of the informed patient sharing in decision making. If we practice what we preach, physicians must let frightened women know that, even without screening, most women who get breast cancer will not die of it and that, despite screening, some women will still die of breast cancer. Some physicians may even draw attention to the mortality paradox. Women will continue to be misled if they remain incompletely informed. Women must demand that research soon provide the answers.

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NOTE

Manuscript received February 10, 2003; revised March 21, 2003; accepted June 4, 2003.