The Great Mammography Debate

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Controversy is only dreaded by the advocates of error.
—Benjamin Rush

Screening mammography saves lives. This statement is not controversial to clinicians who diagnose and treat breast cancer on a daily basis and, as the authors have, for over 40 combined years. There are numerous randomized controlled trials that have demonstrated the mortality benefit of screening mammography. The trial with the longest follow-up period[1] and the largest trial[2] have both demonstrated a nearly one-third reduction in breast cancer-specific mortality in screened women. In the United States, data from the Surveillance, Epidemiology, and End Results (SEER) program revealed a 30% decline in breast cancer–specific mortality between 1990 and 2010.[3] The death rate had not changed for 50 years previously. This reduction in mortality parallels the popularization and adoption of screening mammography and is directly attributable to secondary prevention. The controversy over mortality benefits from screening arise principally from a single trial, the Canadian National Breast Screening Study (CNBSS), which is an outlier trial in that it failed to demonstrate any benefit of mammography over clinical breast exam.[4]

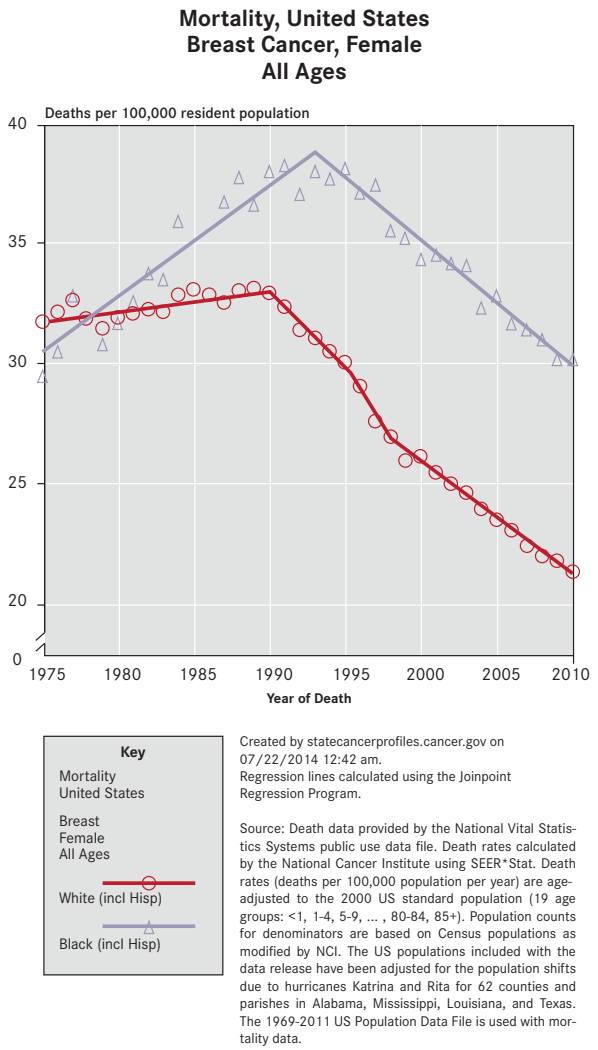
Since then, numerous articles have highlighted a variety of potentially serious flaws and confounding factors in the Canadian study. The debate was recently rekindled when the 25-year results of the CNBSS were published in the *British Medical Journal*.[4] Again, the long-term follow-up failed to demonstrate benefit from mammographic screening for breast cancer over simple clinical breast examination. This conclusion would appear to be at odds with virtually all other screening trials, clinical experience, and good old-fashioned common sense (**Figure**).

The Canadian National Breast Screening Study

The efficacy of screening mammography was evaluated in randomized trials in the 1970s and 1980s. A decade ago, an overview by the World Health Organization indicated that mammographic screening appeared to reduce mortality from breast cancer by 25%.[5] However, a report from the Cochrane Collaboration questioned the estimates of mortality benefit from many of the original trials.[6] The contrarian view—that mammographic screening did not impact survival—was largely fueled by the findings of the CNBSS, which found no reduction in breast cancer mortality in women undergoing mammography. (In fact, the screened arm had a higher mortality rate from breast cancer than the control group.)

The CNBSS was conceived in the late 1970s and begun in 1980, and was a direct response to the only large-scale breast cancer screen-

FIGURE. Historical Trends (1975-2010)



Mortality (deaths per 100,000 women, all ages) from breast cancer in the United States, 1975 to 2010, from the National Vital Statistics System and the SEER program. The downturn in mortality rates that commenced between 1990 and 1994 correspond to the beginning of the popularization and adoption of screening mammography, and is therefore attributable to secondary prevention. This improvement in survival predated advances in systemic therapy such as anthracycline-based chemotherapy, taxane-based chemotherapy, and trastuzumab.

ing study in existence at that time—the New York Health Insurance Plan (HIP) Study.[7] In 1963, the HIP study randomized 60,000 women between the ages of 40 and 64. Nearly 30,000 women received annual two-view mammography and clinical breast examination for three screens, with another 30,000 women serving as controls who received "usual care" (ie, clinical breast examination). The results were first published in 1977 and indicated a statistically significant reduction in breast cancer mortality of 23%. However, no benefit was seen in women in the age 40-49 group. Also, over an 8-year period after diagnosis, breast cancer cases that were identified only on mammography when screened had a case fatality rate of 14%, as compared with 32% for cases positive only on clinical examination and 41% for cases identified via both modalities. The apparent lack of mortality benefit in the women aged 40-49 was partially attributable to the relative rarity of breast cancer in that age group. These findings led directly to the design and implementation of the CNBSS.

The objective of the CNBSS was to compare breast cancer incidence and mortality with a follow-up of up to 25 years in women aged 40-59 who did or did not undergo mammographic screening.[4] This was not a population-based study but rather involved healthy volunteers who attended screening center programs in six Canadian provinces. A total of 89,835 women, aged 40-59 years were assigned to a group that received annual mammography (5 annual mammography screens) or to a control group that received no mammography. Women aged 40-49 in the mammography arm and all women aged 50-59 in both arms received annual physical breast examinations. Women aged 40-49 in the control arm received a single examination followed by usual care in the community. All patients had a clinical breast examination *prior* to group assignment. Patients in whom a suspicious finding was identified (symptomatic patients) were *not excluded* from trial participation. The published patient-specific data comparing the two groups suggest that some patients with palpable findings were preferentially assigned to the mammographic screening arm of the trial. This has been disputed by the Canadian trialists. There is universal agreement, however, that these symptomatic patients should have been excluded from this screening trial altogether. Screening trials, to be valid, are exclusively designed for asymptomatic patients.

During the 5-year screening period, 666 invasive breast cancers were diagnosed in the mammography arm (n=44,925 participants) and 524 in the controls (n=44,910), and of these, 180 women in the mammography arm and 171 women in the control arm died of breast cancer during the 25-year follow-up period. The substantially higher number of breast cancers in the mammography arm has been used as evidence to suggest that assignment to the screening arm occurred in patients with physical findings. Moreover, the overall hazard ratio (HR) for death from breast cancer diagnosed during the screening period associated with mammography was 1.05 (95% confidence interval [CI], 0.85-1.30). The findings for women aged 40-49 and 50-59 were almost identical. During the entire study period, 3250 women in the mammography arm and 3133 in the control arm had a diagnosis of breast cancer, and 500 and 505, respectively, died of breast cancer. Thus, the cumulative mortality from breast cancer was similar between women in the mammography arm and in the control arm (HR = 0.99; 95% CI, 0.88-1.12).

The authors concluded that annual mammography in women aged 40-59 years does not reduce mortality from breast cancer beyond that of physical examination or usual care. They postulated that advances in systemic therapy balanced the differences in stage at diagnosis. Overall, the authors argued that 22% (106/484) of screen-detected invasive breast cancers were overdiagnosed, representing 1 overdiagnosed breast cancer for every 424 women who received mammography screening in the trial. Use of the term *overdiagnosis* is primarily applicable to noninvasive breast cancers. Its use in invasive cancers is controversial and difficult to prove. It is also true that, even with aggressive cytotoxic and endocrine ablative treatment approaches, there is considerable difference in survival across the spectrum of stage I, stage II, and stage III breast cancer. Early diagnosis and effective intervention matter in breast cancer.

CNBSS Limitations

Poor Image Quality

One explanation for the results of the CNBSS is poor image quality. It stands to reason that there is an inverse relationship between image quality and cancer detection performance. It is *also* worth bearing in mind that the x-ray equipment used in this study was standard technology *for 34 years ago*, as the screening took place from 1980 to 1985. No imaging grids such as the ones used today nor conventional orthogonal views were employed. There was no training for many of the mammography technicians, and there was no (apparent) quality control employed in the study. Daniel Kopans, MD, was one of the experts called upon in 1990 to review the quality of the mammograms. He has publicly stated that the quality was poor.[8] The images were compromised by scatter artifact, and the breasts were not uniformly positioned in the x-ray machines. The CNBSS's own reference physicist wrote, "…in my work as reference physicist to the [CNBSS, I] identified many concerns regarding the quality of mammography carried out in some of the [CNBSS] screening centers. That quality [in the CNBSS] was far below state of the art, even for that time (early 1980's)."[9]

Poor image quality and lack of expertise in interpretation is clearly evidenced by the fact that only 32% of the cancers were detected by mammography alone. By conventional standards, at least two-thirds of the cancers should be detected by mammography alone. This is not a trivial point, as poor mammographic technique means inability to visualize small, potentially fatal cancers. In an accompanying editorial, Kalager et al[10] state that "The lack of mortality benefit is also biologically plausible because the mean tumour size was 19 mm in the screening group and 21 mm in the control group….a 2 mm difference." Poor quality mammography does not find breast cancers at a smaller size and earlier stage and would not be expected to reduce deaths.

Study Subject Allocation Bias Allegations

The documented poor quality of the CNBSS mammography is suf-

ficient to explain the results and, in and of itself, would disqualify the CNBSS as a scientific study of mammography screening. However, the problems of image quality were further compounded by alleged deviation from patient randomization protocols. In order to be valid, randomized, controlled trials (RCTs) require that assignment of the patients to the screening group or the unscreened control group is totally random. A fundamental rule for an RCT is that nothing can be known about the participants until they have been randomly assigned so that there is no risk of compromising the random allocation.[11]

In the Canadian study, every woman first had a clinical breast examination by a trained nurse (or doctor). It is reasonable to postulate that (some) symptomatic patients (those with abnormal breast or axillary examination) may have been preferentially assigned to the screening mammography arm of the trial. If this occured it would represent a major trial violation. Moreover, instead of a random system of assigning the women to each subgroup, open lists were employed that may have allowed the insertion of names at the discretion of the study coordinators. There would likely be more early deaths among the screened women than the control women as a result of this, and this seems to be the case in the CNBSS.

Impact of the CNBSS

In a surprising move, the Swiss Medical Board, which is an independent health technology assessment consortium, recently reviewed the evidence for breast cancer screening and made recommendations to the government of Switzerland. The Board noted that the current debate on the benefits and harms of mammography screening is based on "outdated randomized controlled trials (RCTs)" and that it was "non-obvious" that the benefits of mammographic screening outweighed the harms. They recommended that no new mammography screening programs should be introduced in Switzerland, and that the existing ones should be phased out as funding cycles end.[12]

In making this decision, the Swiss Medical Board relied on a review by another panel: the Independent United Kingdom Panel on Breast Cancer Screening. This group used data from selected published RCTs. Based on their analysis, the UK panel estimated that for every 10,000 women aged 50 years invited to screen for the next 20 years, approximately 43 women would avoid a death from breast cancer and the remaining 9957 would receive no mortality benefit. Stated in another way, 4 women per 1000 per year would have their lives saved by getting a mammogram.[13] This analysis did not take into consideration the typical morbidity associated with treating cancers at a later stage.

There are three questions raised by the actions of the Swiss Medical Board:

1. Are the data used to make this landmark decision reliable? This question has been answered in the previous sections.

2. How does the investment in mammography per lives saved compare with other societal investments in saving lives? Automobile seat belts, at about $25 per installation, are one of the most cost-effective lifesaving devices ever invented. In a given year, it costs roughly $500 million to put seatbelts in every US vehicle, which translates to a rough estimate of $30,000 for every life saved. At current rates, 1000 screening mammograms cost the healthcare system $100,000, or $25,000 per life saved, which is comparable to the dollars per life saved with seatbelts. At an annual US price of more than $4 billion, air bags cost about $1.8 million per life saved or 72 times more expensive in saving lives than mammography. There has been no indication that Switzerland is planning to remove seatbelts from automobiles.

3. Is mortality the only valid endpoint when evaluating screening mammography? Certainly there would be value in reducing the need for aggressive, morbid treatments such as mastectomy, cytotoxic chemotherapy, and/or radiation therapy? Screening mammography finds cancer (for the most part) in its earliest stages, allowing tumors to be detected at a smaller size, with less axillary nodal involvement. Plecha et al[14] reported that, in women participating in screening mammography programs, in addition to the benefits of receiving a diagnosis at earlier stages, with smaller tumors and axillary nodes that are free of metastases, patients with breast cancer undergoing screening mammography aged 40-49 years are less likely to require chemotherapy and its associated morbidities and long-term risks. In their study, the majority of high-risk lesions were diagnosed in the screened group, which may lead to the benefit of chemoprevention, lowering their risk of subsequent breast cancer. Patients in the screened group had a lower likelihood of requiring mastectomy, as well.

Foca et al[15] reported a significant and stable decrease in the incidence of late-stage breast cancer as early as the third year of screening, at which point the calculated incidence rate ratio fell from 0.81 to 0.71. Finally, Malmgren et al[16] reported a significant increase in the percentage of nonpalpable, mammogram-detected breast cancers over time and a concurrent decline in patient/physician-detected breast cancers (P =.001). Screen-detected breast cancer patients were significantly more likely to undergo breast conservation rather than mastectomy (67% underwent lumpectomy in the mammogram group, 48% in the patient/physician detected group; P =.001). Significantly fewer patients in the screen-detected breast cancer group required postsurgical chemotherapy.

Conclusion

Twenty-one years ago, Boyd and colleagues[17] published the following conclusion about the CNBSS: "Taken at face value, the results of the CNBSS argue for abandoning mammographic screening as a population-based means of controlling death rates from breast cancer. We believe such a conclusion to be unjustified and unsupported by the findings of the CNBSS…the results of these trials should not be used to change the prevailing scientific view of the potential benefits of screening with mammography." Much has been learned in the ensuing 20 years, and much data have been generated. The inevitable conclusion is that Boyd's statement is truer today than ever.

Mammographic screening saves lives. Moreover, mammographic

screening for breast cancer reduces the morbidity of required treatment approaches and improves the chances for a favorable long-term outcome. Mammographic screening often gives patients diagnosed with breast cancer *options*.

It is high time that mammographic screening for breast cancer be evaluated and appraised using the same metrics and benchmarks used to screen for other solid tumors. Studies that are confounded should be excluded from analyses that will impact critical decision making. It is incorrect to assume that the treatments for breast cancer have evolved to the point that stage at diagnosis is irrelevant. Women destined to develop breast cancer have every right to value and expect the earliest possible diagnosis of their disease.

Finding and treating breast cancer at the earliest possible stage remains a vitally important weapon in our war against breast cancer, and screening mammography remains the most important cornerstone against which all breast cancer treatments find their foundation.

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