

ORIGINAL ARTICLE

Screening Mammography Controversies: Resolved, Partly Resolved, and Unresolved

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■ **Abstract:** Since the 1960s, multiple randomized clinical trials have measured differences in breast cancer mortality between women 40 and 70 years of age who were offered screening mammography and control group women. This article describes briefly these trials, which nearly universally documented statistically significant reductions in breast cancer deaths. These trials also underestimated the benefit, regardless of age, due to screening parameters that were not optimized. In recent years, published articles analyzing studies of Swedish women have claimed that there is no reduction in overall mortality from breast cancer and other causes among women offered screening. Critical assessment of these articles noted that breast cancer deaths were less than 5% of all deaths and that no statistically significant reduction in overall mortality rates should be expected within the population that had been analyzed. The latest screening mammography controversies involve potential adverse consequences and risks, such as X-ray exposure, detection of ductal carcinoma in situ (DCIS), and “excessive” callback rates for additional imaging studies. Despite these controversies, the preponderance of scientific evidence continues to strongly support annual screening mammography for women 40 years of age and older. ■

Key Words: breast cancer mortality, mammography, screening

RANDOMIZED TRIALS PROVE SUBSTANTIAL BENEFIT

Seven randomized trials conducted during the past 40 years have measured deaths from breast cancer among study group women 40–70 years of age offered screening mammography and control group women (1,2). Six randomized trials found that screening reduced breast cancer mortality in the entire range of ages screened. In three randomized trials (HIP, Swedish Two-County, and Edinburgh) there were statistically significant reductions in breast cancer deaths of 23%, 32%, and 29%, respectively (3–5). Three other randomized trials (Malmo, Stockholm, and Gothenburg, Sweden) reported nonsignificant reductions of 19%, 20%, and 14%, respectively (6–8). Only one trial, the National Breast Screening Study of Canada (NBSS) was unable to demonstrate any benefit from screening (9,10). Their results may be explained by extremely poor technical quality and a faulty randomization scheme (11).

At early follow-up, no trial showed much benefit for the subset of women who entered screening between the ages of 40 and 49 years. Benefit for these younger women

took longer to appear because their breast cancer growth rates were faster and their screening intervals excessively long (12–14). As a consequence of the relatively small number of younger women enrolled and their lower incidence of breast cancer, initial proof of benefit required pooling results from multiple trials in order to attain statistical significance. By 1997, a meta-analysis of women age 40–49 years at entry into all five Swedish trials found a significant 30% reduction in breast cancer deaths (15). Subsequent long-term follow-up of the younger women in three individual trials—HIP, Gothenburg, and Malmo—each found statistically significant breast cancer mortality reductions of 24%, 45%, and 36%, respectively (16–18). Thus benefit for screening women ages 40–49 and 50–70 years became well established.

Every trial underestimated the benefit for women of all ages because screening parameters were not optimized. Deficiencies included excessively long screening intervals, incomplete study group participation, control group contamination, one versus two views per breast, and sub-optimal technique and interpretation (12–19).

SERVICE SCREENING FINDS EVEN GREATER BENEFIT

Based on the success of the randomized trials, many Scandinavian counties now offer screening mammography as a public health service to women age 40 years and

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older. Five studies from Sweden and one from Finland have shown that “service screening” has been associated with a reduction in breast mortality often exceeding that found by the randomized trials (20). In the counties of the Swedish Two-County Trial, subsequent service screening of women age 40–74 years reduced breast cancer deaths by 50% among those offered screening and 63% among those who agreed to be screened (21). Similar results were found in an expanded study of seven Swedish counties (22).

THE GOTZSCHE AND OLSEN FIASCO: A CONTROVERSY THAT FIZZLED

Several years ago, the results from randomized trials were questioned by P. C. Gotzsche and O. Olsen, who claimed that there was no reduction in overall mortality (deaths from breast cancer plus all other causes combined) among Swedish women offered screening (23,24). Critics of the Gotzsche and Olsen study were quick to point out that deaths from breast cancers represent less than 5% of all causes of death. Thus no statistically significant reduction in overall mortality rates should be expected within the population size examined. Nevertheless, Tabar et al. (25) were able to demonstrate a reduction in all-cause mortality among breast cancer patients offered screening compared to those who had not been offered screening.

Gotzsche and Olsen also argued that an age imbalance between study and control groups in several Swedish trials invalidated their results. Age differences, however, were small. Some lead to a slight underestimate, while others resulted in a slight overestimation of benefit. The overall effect was negligible (26,27). Moreover, age imbalance is practically unavoidable in screening trials where women, by standard practice, are randomized by clusters. Screening trials are different from therapeutic trials for which randomization by individuals is preferable. Randomization procedures in the Swedish trials were both well designed and executed and have been intensively described in the literature. Numerous other flaws in the Gotzsche and Olsen studies have been detailed in the literature (26,27).

In summary, the weight of scientific evidence strongly supports annual screening mammography of all women 40 years of age and older (2). The Gotzsche and Olsen articles became headline news on television and in newspapers and magazines, but were subsequently repudiated by virtually all U.S. and international medical organizations, such as the American Cancer Society, the Swedish and Danish National Boards of Health, and the World Health

Organization. Upon review, these organizations reaffirmed the validity of results from screening trials (26,27).

RADIATION RISK

The latest screening mammography controversies involve potential adverse consequences and risks such as X-ray exposure, detection of ductal carcinoma in situ (DCIS), and “excessive” callback rates for additional imaging studies (28). Potential radiation risk from mammography is a persistent concern for some women. However, at the current dose of about 0.4 rad per exam, the risk from radiation is negligible compared to the benefit from screening, even for annual mammography beginning at age 40 years (29). A recent report from the National Council on Radiation Protection and Measurements (NCRKP) concludes that mammography is safe and that the proven reduction in breast cancer mortality through screening far outweighs the hypothetical risk from radiation (30).

DETECTION OF DCIS: BENEFIT OR HARM?

Coincident with the widespread utilization of mammography, there has been a marked increase in the incidence of DCIS. Prior to the screening era, DCIS represented less than 5% of all malignancies of the breast (31). Today, DCIS accounts for 20–40% of nonpalpable cancers detected at screening (32–34). With appropriate treatment, the survival rate for DCIS should be 99.5% (35,36). DCIS may be considered a nonobligate precursor of fatal breast cancer. All cases of invasive ductal carcinoma are believed to develop from DCIS. Yet it is not certain that all cases of DCIS progress to invasive carcinoma.

Any assumptions regarding the natural history of untreated DCIS carry significant clinical implications. Women with DCIS undergo further imaging examinations, biopsy, lumpectomy, or mastectomy, and are frequently treated with radiation or chemotherapy. How often is DCIS overtreated? Does the benefit from detection of some cases outweigh the risks of biopsy and treatment of other cases? These legitimate questions have been raised by several observers (34,37–40). There is, however, a growing body of evidence that detection of DCIS is a major component of the benefit from screening (41). As Cady has said “currently there is one presumed method to prevent invasive breast cancer, detect and evaluate ductal carcinoma in situ” (42).

The invasive potential of DCIS has been calculated from screening studies. Based on data from five different

screening programs, Yen *et al.* (43) estimated that among cases of DCIS detected at initial screening, 63% were progressive and 37% were nonprogressive. At incidence (subsequent) screens, 96% of detected cases of DCIS were progressive and 4% were nonprogressive.

The average transition time from nonprogressive DCIS to invasive cancer among women age 40–49 years in the Swedish Two-County Trial was estimated at 11.6 years (43). Thus, for younger women, even detection of nonprogressive DCIS will have an intermediate-term benefit.

SCREENING CALLBACK RATES

Several recent studies have shown that “false positive” mammograms, where patients are called back for additional imaging, are more common in the United States than Europe, even though our detection rates are no higher (44,45). The implication that U.S. radiologists are calling back too many patients ignores the effect of differences in breast cancer incidence rates and risk factors between the two continents. These factors all influence recall rates. More importantly, detection rates for early cancers and overall breast cancer survival rates are higher in the United States (28,46,47). Largely due to the widespread utilization of screening mammography, the average patient with invasive breast cancer in the United States today is 39% less likely to die from her disease than was her counterpart in the early 1980s (20).

SCREENING GUIDELINES

Screening mammography beginning at age 40 years is currently advised by the American Cancer Society (ACS), American College of Radiology (ACR), National Cancer Institute (NCI), the American College of Obstetrics and Gynecology (ACOG), the American Society of Breast Disease, and the U.S. Preventive Services Task Force (USPSTF) (1,2,48,49). For women age 40–49 years, the ACS, ACR, and ACOG advise annual screening. NCI and USPSTF advise screening every 1–2 years. All the organizations advise annual screening for women age 50 years and older.

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