

Breast Cancer Screening: Understanding the Randomized Controlled Trials

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Screening mammography has been shown to decrease breast cancer mortality across multiple trials, and across many different study designs. Despite this, some opponents continue to question the value of mammography. Thus, it is increasingly important that breast imaging care providers understand the nature and results of the randomized controlled trials (RCTs), which have definitively demonstrated that screening mammography in women 40-74 years of age decreases deaths from breast cancer.

Cancer localized in the breast is not what causes death; it is breast cancer spread (metastasis) to other organs that causes mortality. The goal of mammographic screening (and other breast cancer screening tests) is to detect breast cancer earlier than it would otherwise manifest clinically, when it is less likely to have spread. Data clearly show that detection of breast cancers at smaller sizes and lower stages is associated with better patient outcomes from lower morbidity and reduced breast cancer deaths.

RCTs are the gold standard for proving that early detection with mammography decreases mortality from breast cancer. It is important to understand that the key evidence measure is the breast cancer death rate observed in the experimental group (women invited to have screening mammography) compared to that in the control group (women not invited to have screening mammography). It is not sufficient to use survival time (the time of discovery of the cancer to the date of death) between the groups, as this may reflect “lead-time” bias, in which a cancer is found earlier so survival time appears longer, but the date of death is not altered. RCTs avoid “lead-time” bias and have shown that the primary benefit of screening is decreased breast cancer mortality rates.

RCTs for screening mammography are performed by assigning, in a blinded fashion (randomizing), women into two identical groups, the experimental group (women invited to screening mammography) and the control group (women not invited to screening). When properly randomized, the same number of women in the experimental and control groups will develop breast cancers over the years, and if no screening were done in either group, the same number of women would die of breast cancer in each group. In effect, every woman has an equivalent “twin” in the opposite group. If a woman in the experimental group develops and dies from a breast cancer then her “twin” in the control group will die from breast cancer. If screening works, long-term surveillance after the intervention period will show that the breast cancer death rate in the invited group is less than the breast cancer death rate in the control group. The difference in the breast cancer death rates between

these two groups determines the mortality reduction from mammography screening.

The first RCT of screening mammography (Health Insurance Plan, or HIP Trial) was performed in New York in the 1960s (1). The HIP Trial demonstrated a 23% decrease in the death rate in women who were invited to screening. Seven additional prospective RCTs were performed after the HIP trial. The individual trials, as well as numerous subsequent meta-analyses combining trial results, continue to demonstrate a mortality reduction from mammography screening of 15-30%.

In fact, the mortality benefit to women screened regularly is actually greater. RCTs underestimate the mortality benefit of screening. RCT analyses include women in the "invited to screen" group who did not actually undergo mammography (non-compliance). If they died from breast cancer they have still been counted as a death among the "screened" women. This increases the death rate in the invited group. On the other side of the coin, there were women in the "not invited to screen" group who had mammography on their own, outside of the trial (contamination). They may have had their lives saved by that mammogram but are still counted with the "unscreened" controls. This decreases the death rate in the unscreened group. Together, non-compliance in the screened group and contamination in the unscreened group decrease the observed difference in breast cancer mortality in the RCTs. As a result, the true mortality benefit of screening mammography is even greater than what has been shown in the RCTs.

Smith et al published an excellent summary of the RCTs (2). All demonstrated a substantial reduction in the death rate from breast cancer in women invited to undergo screening mammography, with the exception of the Canadian National Breast Screening Study (CNBSS) (3,4). The flaws in the CNBSS study have been described in peer-reviewed publications (5-8) and will be discussed in depth in a subsequent article.

Although all of the mammography screening trials have some limitations, RCTs consistently demonstrate a reduction in breast cancer deaths of 15-30% in women 40 to 74 years of age invited to screening mammography. Unfortunately, in an often quoted study by Gotzsche and Olsen, all but two of the RCTs are excluded from the analysis (9). The Gotzsche and Olsen papers overstate the limitations of the studies that they excluded and ignore the flaws of the CNBSS.

To summarize, all of the well-executed RCTs have demonstrated that screening mammography decreases breast cancer deaths, proving the importance of early detection: breast cancers can be cured if detected and treated early.

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2. [Smith R, Duffy S, Gabe R, Tabar L, Yen A, and Chen T. The randomized trials of breast cancer screening: what have we learned? Radiol Clin North Am 2004;42\(5\):793-806](#)
3. [Miller AB, Baines CJ, To T, Wall C. Canadian National Breast Screening Study: 1. Breast cancer detection and death rates among women aged 40 to 49 years. CMAJ 1992;147:1459-76. PMID:1423088.](#)
4. [Miller AB, Baines CJ, To T, Wall C. Canadian National Breast Screening Study: 2. Breast cancer detection and death rates among women aged 50 to 59 years. CMAJ 1992;147:1477-88. PMID: 1423087.](#)
5. [Burhenne LJ, Burhenne HJ: The Canadian National Breast Screening Study: A Canadian critique. Am J Roentgenol 1993; 161:761-763.](#)
6. [Kopans DB, Feig SA: The Canadian National Breast Screening Study: A critical review. Am J Roentgenol 1993; 161:755-760.](#)
7. [Tarone RE: The excess of patients with advanced breast cancers in young women screened with mammography in the Canadian National Breast Screening Study. Cancer 1995; 75: 997-1003.](#)
8. [Heywang-Kobrunner SH, Schreer I, Hacker A, Hoftz MR, Katalinic A. Conclusions for mammography screening after 25-year follow-up of the Canadian National Breast Cancer Screening Study \(CNBSS\). European Radiology 2016; 26\(2\):342-50.](#)
9. [Gøtzsche PC, Olsen O. Is screening for breast cancer with mammography justifiable? Lancet. 2000; Jan 8;355\(9198\):129-34. PMID: 10675181](#)