

S19. Validity of Screening Mammography Trials

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Seven randomized trials (RCT's) conducted during the past 40 years have measured deaths from breast cancer among study group women offered screening mammography and control group women. Six RCT's found that screening reduced breast cancer mortality in the entire range of ages screened. For 3 RCT's (HIP, Swedish Two-County, and Edinburgh) there were statistically significant reductions in breast cancer deaths of 23%, 32%, and 29% respectively. The Malmo, Stockholm, and Gothenburg Sweden trials reported non-significant reductions of 19%, 20%, and 14% respectively. Neither arm of the National Breast Screening Study of Canada (NBSS) was able to demonstrate benefits from mammographic screening.

Early follow-up found only uncertain benefit for the subset of women who entered screening between the ages 40-49 years. Because breast cancer growth rates were faster in this age group and screening intervals excessively long, benefit did not appear until seven years of follow-up. Even then, due to the relatively small number of younger women enrolled and their lower incidence of breast cancer, combined results from several trials were initially necessary to attain statistical significance. By 1997, a meta-analysis of women age 40-49 years at entry into all 5 Swedish trials found a significant 30% reduction in breast cancer deaths. Three individual trials: HIP, Gothenburg, and Malmo found breast cancer mortality reductions of 24%, 45%, and 36%.

Because screening parameters were not optimized at any RCT, it is likely that benefits for women of all ages screened were underestimated. Deficiencies present at one or more trials included excessively long screening intervals, incomplete study group participation, control group contamination, 1 vs 2 views per breast, and sub-optimal technique and interpretation. The extremely poor technical quality of mammography at the NBSS was documented long before their negative clinical results were published. There were also findings suggestive of randomization errors at the NBSS.

Until recently, the efficacy of screening mammography had only been challenged for women age 40-49

years. Within the past 2 years several articles have questioned the benefits from screening women at any age. One study by Sjonell and Stahl found no reduction of breast cancer deaths among all Swedish women despite widespread service screening. This study has been criticized because the time period for which death rates were measured came too soon after and in some cases even before service screening had been implemented.

Four studies from Sweden (Jonsson et al, Garne et al, Lenner et al, Tabar et al) and one from Finland (Hakama, et al) have shown that service screening was associated with reduction in breast mortality comparable to or greater than results from RCT's. Analysis of service screening by Tabar et al from the 2 counties that had been in the Swedish Two-County Trial, found that reduction breast cancer deaths were reduced 50% among women ages 40-74 years offered screening and 63% among those who were screened.

This past year, one study by Gotzsche and Olsen was unable to find any reduction in overall mortality from breast cancer plus all other cancers combined among Swedish women offered screening. Critics of this study were quick to point out that because death from breast cancers represent less than 5% of all deaths for these age groups, that no statistically significant reduction in overall mortality rates should be expected within the population size examined.

Gotsche and Olsen also suggested that an imbalance between study and control groups in the Swedish trials invalidated their results. If anything, an older age of study group women would lead to an underestimate of benefit from screening. Moreover, with cluster randomization such age imbalance is practically unavoidable and should be expected. Screening trials are different from therapeutic trials where 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. In summary, the weight of scientific evidence continues to strongly support annual screening mammography of all women from age 40 years.