Evidence to Support Screening Women in Their 40s

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KEYWORDS

• Mammography • Screening • 40 to 49 • Evidence • Controversy

KEY POINTS

- A large body of evidence demonstrates a 30% to 50% mortality benefit of screening mammography for women aged 40 to 49.
- Because of more rapid cancer growth rates in younger women, annual screening is more effective than biennial.
- Selective screening of women aged 40 to 49 based on risk factors to minimize harms would miss the majority of breast cancers.
- If implemented, recent US Preventive Services Task Force (USPSTF) breast cancer screening guidelines, which recommend against routine screening of women in their 40s, could result in thousands of preventable breast cancer deaths per year.

BREAST CANCER DISEASE BURDEN IN WOMEN AGED 40 TO 49

The incidence of breast cancer in the United States increases significantly at approximately age 40 and rises steadily with increasing age thereafter. Based on 2009 to 2013 data from the Surveillance, Epidemiology, and End Results Program of the National Institutes of Health, the annual incidence rises from approximately 0.3 to 0.6 per 1000 women between ages 30 to 39 to 1.2 to 1.9 per 1000 between the ages of 40 and 49, subsequently increasing to 2.2 to 2.6 for women aged 50 to 59 and 3.4 to 4.2 for women aged 60 to 69.[1] In 2015, there were 48,160 women aged 40 to 49 diagnosed with breast cancer in the United States, which accounts for approximately 17%, or 1 in 6, of all breast cancer diagnoses.[2] Moreover, an estimated 40% of the years of life lost to breast cancer can be attributed to women diagnosed while in their 40s.[3] Thus the breast cancer disease burden among women aged 40 to 49 is substantial.

EFFICACY AND EFFECTIVENESS OF SCREENING MAMMOGRAPHY IN WOMEN AGED 40 TO 49

Multiple study types exist to assess the impact of a screening study. The most rigorous and informative studies, randomized controlled trials (RCTs) and observational studies, deserve particular attention.

Randomized Controlled Trials — Overview

The underlying premise of screening is that early detection and treatment can interrupt the natural history of a disease and prevent a patient's death. Early diagnosis per se, however, does not

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necessarily guarantee a benefit. Merely finding a cancer earlier may not alter its long-term outcome. A screened patient may seem to have longer survival relative to the unscreened, but this could reflect earlier diagnosis without a corresponding delay in the time of death. Such a phenomenon is referred to as lead-time bias. In addition, screening may preferentially detect some indolent lesions, a phenomenon referred to as length-biased sampling. Because of these potential biases, the only way to prove efficacy of a screening test is to evaluate mortality as an endpoint in the setting of a RCT.

Seven population-based RCTs of screening mammography alone or in combination with physical examination were conducted in the United States and Europe from the 1960s to 1980s, which included women aged 40 to 49 at time of trial entry. In addition, a single non–population-based RCT, the Canadian National Breast Screening Study-1 (CNBSS-1), in which women volunteered to participate, was conducted in the 1980s. Meta-analyses at 10-year to 18-year follow-up have shown statistically significant mortality reductions for women aged 40 to 49 at invitation of 24% in the 7 population-based RCTs, 29% in the 5 Swedish RCTs, and 15% to 18% in all 8 RCTs (including CNBSS-1) (**Table 1**).[4–6] At subsequent 12-year to 13-year follow-up of 2 Swedish trials, statistically significant mortality reductions of 45% and 36%, respectively, were found for women aged 39 to 49 years at randomization in the Gothenburg breast screening trial and for women aged 45 to 49 years at entry in the Malmö mammographic screening program trial (see **Table 1**).[7–9]

Table 1
Randomized controlled trials of screening mammography showing statistically significant breast cancer mortality reduction on long-term follow-up for women aged 40 to 49 years

Trial	Follow-up (y)	Mortality Reduction (%)[a]
All 8 RCTs	10.5–18.0	15–18
7 RCTs (excluding CNBSS-1)	7.0–18.0	24
5 Swedish trials	11.4–15.2	29
Gothenburg, Sweden	12.0	45
Malmö, Sweden	12.7	36

[a] Statistically significant mortality reduction at 95% CI.

Randomized Controlled Trial Controversy

Controversy first arose over screening of women in their 40s when a retrospective subgroup analysis was performed for the first RCT, the Health Insurance Plan (HIP) trial of New York, conducted in the 1960s. Using age 50 as a surrogate for menopause, the investigators evaluated mortality benefit separately for women aged 40 to 49 and 50 to 64. Initial results at 4 years' follow-up (an extremely short follow-up interval) failed to show a statistically significant benefit for women aged 40 to 49 as there was for women aged 50 to 64.[10] At 18 years of follow-up, a 23% mortality reduction was seen for the 40 to 49 age group, the same relative benefit as for women aged 50 to 64; however, the benefit for women aged 40 to 49 remained statistically insignificant.[10]

The lack of a statistically significant benefit for women aged 40 to 49 was due to the fact that there were not enough women in this age group enrolled in the study to provide the statistical power to detect a benefit.[11] A larger study population was needed given the lower incidence of breast cancer in this age group. Unfortunately, the lack of a statistically significant benefit was erroneously interpreted by many as proof that there was no benefit.[12]

None of the RCTs was designed to evaluate the effectiveness of screening for women aged 40 to 49 years. Therefore, early subset analyses for this age group did not find a statistically significant benefit. Longer-term follow-up, however, eventually compensated for the lack of statistical power. In 1997, after 10-year to 18-year follow-up, meta-analysis of 5 Swedish RCTs yielded a statistically significant 29% mortality reduction for women aged 40 to 49, which was the same relative benefit as for older women.[6] Several individual trials also demonstrated a statistically significant mortality reduction for the 40 to 49 age group, ranging from 23% in a reanalysis of the HIP trial at 18 years of follow-up to 36% to 45% for the Swedish Malmö and Gothenburg trials at 12 years to 13 years of follow-up.[7–9]

Canadian National Breast Screening Study

The CNBSS-1 trial warrants particular attention and review. After the HIP trial, CNBSS-1 was launched in 1980, specifically designed to address the efficacy of screening mammography for women in their 40s. The CNBSS-1 allocated (or randomized) 50,430 female volunteers aged 40 to 49 to undergo annual mammography, clinical breast examination, and breast self-examination; or usual care. After 11 to 16 years of follow-up,