Efficacy of Screening Mammography Among Women Aged 40 to 49 Years and 50 to 69 Years: Comparison of Relative and Absolute Benefit

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In randomized controlled trials, screening mammography has been shown to reduce mortality from breast cancer about 25% to 30% among women aged 50 to 69 years after only five to six years from the initiation of screening. Among women aged 40 to 49 years, trials have reported no reduction in breast cancer mortality after seven to nine years from the initiation of screening; after 10 to 14 years there is a 16% reduction in breast cancer mortality. Given that the incidence of breast cancer for women aged 40 to 49 years is lower and the potential benefit from mammography screening smaller and delayed, the absolute number of deaths prevented by screening women aged 40 to 49 years is much less than in screening women aged 50 to 69 years. Because the absolute benefit of screening women aged 40 to 49 years is small and there is concern that the harms are substantial, the focus should be to help these women make informed decisions about screening mammography by educating them of their true risk of breast cancer and the potential benefits and risks of screening. [Monogr Natl Cancer Inst 1997;22:79–86]

Most experts agree that women aged 50 to 69 years should undergo screening mammography, since randomized controlled trials have shown screening mammography to reduce breast cancer mortality (1,2) and to be relatively cost-effective (3,4) for women in this age group. Whether or not recommendations should be extended to include screening starting at age 40 years remains controversial (5–9). This controversy stems from differences in interpretation of evidence and type of evidence used to evaluate whether screening mammography is efficacious.

Rationale for Using Evidence from Randomized Controlled Trials to Evaluate the Efficacy of Screening Mammography

In evaluating the controversy concerning routine screening mammography for women aged 40 to 49 years, it is important to remember that the goal of screening is to reduce the likelihood of death from breast cancer in a person who has the disease. Randomized controlled trials are the most unbiased means of assessing whether a screening test reduces the likelihood of death in a person who has the disease, and, for this reason, they are considered the gold standard when evaluating the efficacy of screening tests. In the randomized controlled trials of screening mammography, participants were randomly assigned to a screened or nonscreened (control) group to ensure that the screened and nonscreened groups were as alike as possible, so that any differences in outcome that were noted at the end of the trial could be ascribed to screening. In comparison, screening mammography programs and case series, which have no comparison group, are considered uncontrolled intervention studies and hence unsuitable for determining whether mammography decreases breast cancer mortality.

The debate concerning screening mammography among women aged 40 to 49 years has been perpetuated by reports from screening programs and case series claiming improved survival among younger women after initial breast cancer detection by mammography (10–13). Survival statistics favor screening since extra time is added to the interval between breast cancer detection and date of death by the fact that the diagnosis was made early. However, this lead-time in diagnosis may not affect date of death. For example, a 43-year-old woman may have breast cancer detected by mammography and a 45-year-old woman by finding a breast lump. If both women die of breast cancer at the age of 55, the former will have survived 12 years after the breast cancer detection and the latter 10 years. Although the 43-year-old woman lived an additional two years with breast cancer, having her breast cancer detected by screening mammography did not alter her life expectancy compared with the 45-year-old woman since both lived to be age 55. Thus, if survival statistics, rather than breast cancer mortality, are used as an endpoint to evaluate the benefits of mammography screening, it will appear as if screening is beneficial since the results will be unadjusted for time to diagnosis (i.e. lead-time bias).

Detection rates of early-stage cancer are also an inadequate measure of whether screening mammography decreases breast cancer mortality, since most cancers detected by mammography are primarily slow growing. If detection rates of early cancers are used as a surrogate endpoint for breast cancer mortality, it will appear as if screening is beneficial, since the results will be

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unadjusted for rate of disease progression (length bias). Breast cancer is a heterogeneous disease, with some tumors growing relatively quickly, others so slowly that they may never cause breast symptoms, and yet others occurring somewhere in between. Within a year, fast-growing breast cancers may grow from undetectably small to large enough to cause symptoms, so that even annual screening may not detect the cancer—that is, it would be too small to detect by mammography on the first test and would already have become apparent before the next scheduled test. In addition, fast-growing tumors missed by screening are more likely to shorten a woman’s life substantially. Slow-growing breast cancers are more likely to be detected by screening mammography because they exist longer in an asymptomatic state. These slow-growing ones may have little or no impact on life expectancy. In addition, some small tumors detected by mammography metastasize early resulting in advanced stage disease at initial diagnosis (14). In this case, early detection may not be beneficial, even though the breast tumor was detected when it was relatively small.

If we knew the natural history of the various types of breast cancer, as well as their frequency and the length of time each existed in various growth states according to decade of age, it might be possible to correct for length and lead-time biases that are inherent in results from screening programs and case series. However, since this is not the case, only randomized controlled trials can provide an accurate picture of whether screening mammography and the treatment that follows decrease breast cancer mortality.

Results from Meta-Analyses of Randomized Controlled Trials

Meta-analysis is a quantitative approach for systematically combining results of previous research to arrive at conclusions about a body of research (15,16). Meta-analyses provide a more stable estimate of the effect of an intervention and put any one trial result into perspective by examining all similar trials.

There have been several meta-analyses published that combine data from randomized controlled trials in order to quantify the overall impact of screening mammography on breast cancer mortality (1,17–19). One of the earliest meta-analysis by Elwood et al., used the fixed-effects Mantel-Haenszel statistical method to pool published data from six randomized controlled trials of screening mammography and found no reduction in breast cancer mortality in women aged 40 to 49 years seven years after the initiation of screening (17). A more recent meta-analysis combined data from eight randomized controlled screening mammography trials and found similar results (1). Four of the eight trials reported a nonsignificant increase in breast cancer mortality, whereas four reported a nonsignificant decrease, indicating a lack of statistically significant benefit or harm from screening mammography (Fig. 1). When data from the eight studies were combined using statistical methods described by Greenland (20) based on the assumption of fixed effects, the overall summary estimate showed a nonsignificant +2% (95% CI: −18% to +27%) increase in breast cancer mortality seven to nine years after the initiation of screening (Fig. 1).

A separate meta-analysis, using a random-effects statistical method, combined results from the same eight randomized controlled trials and showed similar results with a nonsignificant breast cancer mortality reduction of −5% (95% CI: −23% to +18%) (18). Adjustment for cluster randomization in the Edinburgh trial and the Swedish Two-County trial did not affect the results (18). Importantly, despite the diverse study populations and interventions of the various screening mammography trials, the combined meta-analytic results of the eight randomized controlled trials were found to be homogeneous, indicating little variability of results between the individual trials (1,17,18).

Taken together, the results from the three meta-analyses of the randomized controlled trials are consistent and indicate whether women aged 40 to 49 years underwent routine screening mammography or not, the risk of death from breast cancer was the same for the first seven to nine years after initiating screening.

One meta-analysis of data from randomized controlled trials has taken into account the various lengths of follow-up time after the initiation of screening (1). Combining trials with similar lengths of follow-up time is important, since trials with longer follow-up will have more breast cancer events and will be disproportionately weighted in meta-analyses, thus skewing results in favor of these trials. When published data for women aged 40 to 49 years reported from trials with at least 10 to 12 years of follow-up were examined, four of five studies had a relative risk estimate to the left of one, indicating a reduction in breast cancer mortality; however, all of the confidence intervals overlapped one (Fig. 2). When the five studies were combined using meta-analytic techniques (20), overall there was a trend toward a reduction in breast cancer mortality with an overall nonsignificant reduction of approximately −17% (95% CI: −35% to +6%) (1). Pooled data from the five Swedish trials (Fig. 3A), as well as results from the Health Insurance Plan (HIP) trial, also suggest an emerging benefit from screening mammography in younger women that does not occur for at least 9 to 10 years from the initiation of screening (21–24). If updated, unpublished results from the Gothenburg (25), Stockholm (26), Canadian (27), Malmö I and II (28,29), and Edinburgh trials (28,30) are combined with published results from the Kopparberg and Ös-
In order to minimize selection bias in performing a meta-analysis, it is important that all similar trials are combined. Each of the randomized controlled trials listed in Table 1 is slightly different and could be excluded from a meta-analysis of randomized controlled trials of screening mammography for some aspect of its study design or intervention: some trials, for instance, used one-view mammography instead of two-view mammography, which is considered optimal for women aged 40 to 49 years; others used biennial rather than annual screening, also considered optimal for women aged 40 to 49 years; and others combined clinical breast exam with mammography, making it difficult to assess the independent contribution of mammography. Despite these differences, the confidence intervals for all of these studies overlap each other (Fig. 4), indicating that the results from these studies are not greatly dissimilar and can be combined to summarize the results. Thus, it is not methodologically appropriate to selectively omit any one trial, and doing so may introduce selection bias into the results. If adjustment for length of follow-up, data inconsistencies (32) and selective study exclusions are taken into account, Smart’s results are similar to those previously published (1).

One meta-analysis by C. R. Smart et al. (19), found contrasting results from other published overview analyses (1,17,18). Smart and colleagues reported a 24% reduction in breast cancer mortality among women aged 40 to 49 years who underwent screening mammography. Smart’s meta-analysis varied from other published meta-analyses because results were combined from studies with a wider range of follow-up times (7 to 18 years), unpublished data from the Gothenburg trial were included (28), and results from the Canadian National Breast Screening Study (31) were excluded. As demonstrated above, not stratifying results by length of time from initiation of screening disguises the fact that if screening mammography is effective in women aged 40 to 49 years, its effectiveness only appears 10 years after the initiation of screening (Fig. 3A). Meta-analysts are encouraged to consider unpublished data to avoid publication bias, but the drawback to that is, the findings have not been peer reviewed, they may contain errors and inconsistencies. For example, it is puzzling that the Gothenburg trial, whose study methods have never been published, is the only randomized controlled trial that shows a greater benefit for screening women in their forties than for screening women aged 50 and older (1). Smart omitted the Canadian National Breast Screening Study (31) from his meta-analysis, claiming that, since the study population consisted of volunteers rather than being population-based, it should not be combined with the other trials (19). This seems to be a relatively weak criterion for study exclusion, since it is not obvious that having volunteers as study participants would make it more or less difficult to find a reduction in breast cancer mortality among screened women.
Are Data from Randomized Controlled Trials Conclusive?

Some have argued that it is inappropriate to use meta-analytic techniques to pool data to evaluate the efficacy of screening mammography among women aged 40 to 49 years; that such subgroup analyses are inappropriate when initial screening trials were designed for women aged 40 to 74 years (9). However, this is exactly the purpose of a meta-analysis: to combine data from several trials to obtain a more stable estimate of the effect of an intervention when there are insufficient numbers of subjects in any one trial to yield a meaningful conclusion (15,16). If subgroup analyses by age at initiation of screening are to be discounted, then consideration must be given only to the sole randomized trial specifically designed to address the efficacy of screening mammography in women aged 40 to 49 years, and this trial has yet to show a reduction in breast cancer mortality among screened women (27,31).

Others have argued that the randomized controlled trials of screening are methodologically flawed and should not be used to conclude that mammography is not beneficial for women aged 40 to 49 years. Yet, results from these same trials are used to support mammography screening among women aged 50 to 69 years. A meta-analysis (1) of data in women aged 50 and older from eight randomized controlled screening mammography studies demonstrated an overall significant 27% (95% CI: −37% to −6%) reduction in breast cancer mortality after seven to nine years from the initiation of screening (Fig. 5). Of note, despite differences in types of randomization (cluster, individual), interventions (screening intervals from 12 to 33 months, single-view or two-view mammography, screening with or without clinical breast examination), and study populations, screening mammography trials have consistently demonstrated a reduction in breast cancer mortality among screened women aged 50 to 69 years.

Screening mammography trials are also criticized for using obsolete technology, implying that modern mammography has an increased ability to detect breast cancer in younger women. Several published studies, however, show that the sensitivity of modern mammography, in particular its sensitivity to detect invasive cancer, is still lower for women less than age 50 than for women aged 50 and older, despite improvements in technology (33–38). Still others have argued that screening would be effective in younger women if the interval between each mammographic examination were one year rather than two years (39). Only two trials have screened women aged 40 to 49 years an-
nually (23,31), and there was variability in their findings. The HIP trial showed a nonsignificant reduction in breast cancer mortality among women in the group eligible for screening nine years after the initiation of screening, whereas the Canadian trial found a nonsignificant increase seven years after the initiation of screening. Among women aged 50 and older, whether they are screened annually or biennially, the reduction in breast cancer mortality is the same—that is, more frequent screening does not result in more deaths prevented (1). Therefore, given the differences in tumor biology among younger women, it is optimistic to think that more frequent screening in younger women will necessarily result in the same benefit that is evident in older women. Screening more frequently than every two years will, however, increase the number of unnecessary diagnostic evaluations, the detection of cancers of low malignant potential, and the cost of screening (33).

Lastly, proponents of screening mammography contend that randomized controlled trials have enrolled too few women to demonstrate a statistically significant benefit from screening mammography among younger women. If the explanation was merely lack of statistical power, and the efficacy of screening mammography in younger women was similar to that in older women, then a reduction in breast cancer mortality should begin to appear after four to five years from the initiation of screening, as in women aged 50 to 69 years (Fig. 3B), and should become statistically significant with longer follow-up, that is, the percentage reduction in breast cancer mortality observed at seven to nine years from the initiation of screening among women aged 40 to 49 years should be similar to that reported at 10 to 12 years, but with wider confidence intervals around the point estimate. This does not appear to be the case, since the data do not show a gradual separation of the mortality curves between screened and nonscreened groups (Fig. 3A). In fact, the data show slightly higher breast cancer mortality among screened women the first 10 years after the initiation of screening. Arguing that too few women have been enrolled to demonstrate a statistically significant benefit from screening mammography underscores that breast cancer is not as common in younger women as in older women and that mammography is not as effective in reducing breast cancer mortality in younger women.

In summary, the evidence from pooled results of randomized controlled trials may be interpreted in one of two ways: First, results from meta-analyses provide evidence, even if with low power, that screening younger women provides no benefit the first seven to nine years from the initiation of screening; however, a trend toward reduced mortality emerges after 10 years that appears to be smaller than that observed in older women; or second, results from meta-analyses are collectively inadequate, since these analyses are based on retrospective subgroup analysis. In either case, the scientific evidence to support mass mammography screening for women aged 40 to 49 years is not compelling.

**Why Is the Benefit Among Younger Women Delayed?**

Although pooled results of large randomized controlled trials failed to demonstrate any benefit in women aged 40 to 49 years after seven to nine years of screening (1,17–18), some have argued that the trend toward a reduction in breast cancer mortality that begins after 10 years of screening should not be ignored (5). It is unclear why any potential benefit from screening mammography in women aged 40 to 49 years should be delayed a decade. It could be that some of the breast cancers detected among women who start screening at ages 40 to 49 years are actually detected at or after age 50, when mammography is known to be efficacious. The HIP trial has published screening results by age at detection, and it found that 85% of breast cancers in women who started screening between ages 40 and 49 were diagnosed between ages 45 and 54. Almost all of the decrease in breast cancer mortality among women eligible for screening aged 45 to 49 years at entry in the HIP trial occurred in those who had breast cancer detected at ages 50 to 54 years (40). Furthermore, the majority of women in the Edinburgh and Malmo trials, which also showed no benefit seven to nine years from the initiation of screening but a trend toward a delayed benefit after 10 to 12 years (1,2), were also probably aged 50 or older when their breast cancer was diagnosed, since the youngest age of women at the start of screening was 45 years old. The same rationale has been applied to the Swedish data, since women who started screening at ages 40 to 49 years were offered regular screening mammography with many actually being 50 or older in the ensuing years. Computer modeling of the Swedish breast cancer screening trial data has also suggested that some of the observed decrease (about 30–40%) in breast cancer mortality for women aged 40 to 49 years at trial entry may be attributable to continued screening after women reach age 50 (41,42).

Why is mammography efficacious as early as four to five years after the initiation of screening in older women? One explanation is that, among women aged 50 and older, the sensitivity of mammography to detect invasive cancer is relatively high, resulting in few undetected cancers. This relatively high sensitivity is probably due to two factors: a greater proportion of older women tend to have fatty breast density, which allows easy detection of breast cancer; and tumor growth rates are not as rapid as in younger women, allowing sufficient time for detection of small tumors (33,43). Thus, among women aged 50 and older, mammography detects the majority of tumors and detects them when they are more curable than if they were detected clinically. In contrast, the sensitivity of screening mammography to detect invasive breast cancer is lower among women aged 40 to 49 years compared to women aged 50 and older (75% versus 93%) (33). Conventional thinking has been that this lower sensitivity is due to younger women’s breasts being more radiographically dense. However, only two studies have evaluated the sensitivity of mammography according to radiographic breast density, and both found that breast density did not influence the sensitivity of mammography in women less than 50 years of age (21,33). An alternative explanation is that a greater proportion of invasive breast cancers are aggressive in younger women and therefore grow more rapidly, resulting in more interval cancers between regular screening examinations. This theory is supported by the observation that the sensitivity of screening mammography decreases with increasing tumor size. That is, tumors that are not detected by mammography are larger at clinical presentation than tumors that are mammographically detected. A lower sensitivity for detecting large tumors is more
marked in younger than in older women, suggesting that tumors not detected by mammography in these younger women are especially rapid growing (33). This is further supported by the finding that the sensitivity of mammography decreases rapidly as the length of time between screenings increases (33,44), and by the observation that, among women aged 40 to 49 years, a greater proportion of small tumors detected by screening mammography are associated with positive lymph nodes as compared with older women (14,45). Consequently, among women aged 40 to 49 years, the proportion of slow-growing tumors with a good clinical prognosis detected by screening mammography is probably small, which may account for both the marginal and delayed benefit from screening observed in randomized controlled screening mammography trials. Taken together, these findings suggest that the tumor biology is different in younger than in older women and that the small, delayed benefit observed in the randomized controlled trials for women aged 40 to 49 years may be more of a reflection of the biology of the tumor than of screening mammography.

If the delayed reduction in breast cancer mortality is primarily due to detection of indolent tumors among younger women, such as slow-growing invasive tumors or ductal carcinoma in situ, some of these slow-growing tumors could well be detected satisfactorily at or after age 50 years, providing the same reduction in risk of breast cancer deaths as if the tumors were detected in theirforties. If the delayed reduction in breast cancer mortality is, in part, because some of the breast cancers detected among women who start screening at ages 40 to 49 years are actually detected at or after age 50, this is further evidence that starting screening at age 50 is reasonable.

Absolute Benefit

Reporting the relative risk reduction in breast cancer mortality among women undergoing screening mammography compared to those who do not is not as clinically relevant as reporting the absolute risk reduction due to screening. Reporting the relative risk reduction between screened and nonscreened populations as a percentage obscures differences in the incidence of disease among populations. This is particularly important when the incidence of disease events (e.g., breast cancer deaths) is low, as is the case for women aged 40 to 49 years. The absolute risk reduction or risk difference (difference in risk of dying of breast cancer between screened and nonscreened women) takes into account the underlying incidence of disease events and expresses how much the risk of death from breast cancer is reduced by screening. The reciprocal of the absolute risk reduction is the number needed to screen to prevent one death (46). The number needed to screen is a measure of clinical significance that allows comparison between groups with differing underlying incidence of disease events and quantifies the effort required by patient and physician to prevent one death.

A Markov simulation model that takes into account competing causes of death has been used to determine the number needed to screen to prevent one death if women are screened biennially from ages 50 to 69 years, and the number needed to screen to prevent one death if screening was extended to included annual screening every one to two years for women ages 40 to 49 years (47). Assuming that mammography screening among women who initiated screening at age 50 results in a 27% (1) reduction in breast cancer mortality starting five years from the initiation of screening, it has been estimated that 270 fifty-year-old women would need to be screened biennially for 20 years to prevent one death. This means approximately 2,700 screening mammographic examinations would need to be performed to prevent one death (47). Assuming that all of the delayed benefit in breast cancer mortality among women who initiated screening at age 40 results from detecting cancer before age 50 and that the delayed reduction is at least 16% starting 10 years from the initiation of screening, it has been estimated that 2,500 forty-year-old women would have to be screened every one to two years for 10 years to prevent one death (47). This means between 12,500 and 25,000 screening mammographic examinations would have to be performed to prevent one death. The tenfold difference between younger and older women in the number needed to screen to prevent one death is due to the lower incidence of breast cancer among women aged 40 to 49 years, the delay in benefit from screening and the lower relative risk reduction in breast cancer mortality from screening mammography. If the delayed reduction in breast cancer mortality was as large as 27%, it would still require performing between 7,150 and 14,300 screening examinations on women aged 40 to 49 years to prevent one death (47). Therefore, even assuming an optimistic reduction in breast cancer mortality from screening mammography, the number needed to screen and the total number of mammographic examinations needed to prevent one death is very large for women aged 40 to 49 years.

Conclusion

In summary, based on the results of meta-analyses, there is no reduction in breast cancer mortality seven to nine years after the initiation of screening among women aged 40 to 49 years who undergo screening mammography. There appears to be a delayed reduction in breast cancer mortality 10 years after the initiation of screening, and a proportion of this reduction is benefiting women aged 50 to 59 years rather than women in their forties. It is important to emphasize that if screening mammography is effective in reducing breast cancer deaths among women aged 40 to 49 years, the reduction in deaths does not occur for at least a decade following the initiation of screening and appears to be smaller than the reduction observed in women aged 50 and older. Given that the incidence of breast cancer for women aged 40 to 49 years is lower and the potential benefit from mammography screening smaller and delayed, the absolute number of deaths prevented by screening women in this age group is likely to be much less than by screening women aged 50 and older.

Many people feel that it is acceptable to perform widespread screening mammography in women aged 40 to 49 years despite lack of compelling evidence of benefit, yet proven associated risks (5,39,48–50). In the case of screening mammography, these risks include additional diagnostic evaluations and the associated morbidity and anxiety, the potential for detecting and surgically treating clinically insignificant breast lesions, and the potential false reassurance resulting from having a normal examination (51). Before making a blanket recommendation to all healthy women in an age group to have a screening test, the
benefits of the intervention should be proven and should clearly outweigh the risks (52–54). Because the absolute benefit of screening mammography for women aged 40 to 49 years is small and there is concern that the harms are substantial (55–58), the focus should be to help these women make informed decisions about screening mammography by educating them of their true risk of breast cancer and the potential benefits and risks of screening (59).

References

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Note

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