Should We Recommend Screening Mammography for Women Aged 40 to 49?

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In clinical trials, screening mammography has been shown to reduce mortality from breast cancer by about 25% to 30% among women aged 50 years and older after only 5 to 6 years from the initiation of screening. Among women 40 to 49 years old, the evidence supporting the efficacy of screening mammography is less convincing.

Introduction

In evaluating the controversy over regular screening mammography for women 40 to 49 years old, it is important to remember that the goal of screening is to reduce mortality from breast cancer. As we will discuss below, the benefit of screening is clear for women age 50 years and over, but evidence is less compelling for women 40 to 49 years old. If screening is beneficial for women over 50 years old, why would it not confer the same benefit for women 40 to 49 years of age?

In this article, we review the efficacy of screening mammography by age, based on evidence from randomized controlled trials, and discuss possible explanations for the differential effect of screening mammography in younger vs older women. We also explore the potential risks of performing widespread screening mammography among a population of young women when the incidence of disease is low.

Basis of the Dispute

In 1987, the National Cancer Institute (NCI), along with the American Cancer Society, recommended screening mammography for women in their 40s despite the lack of evidence showing that such screening reduces breast cancer mortality in this age group. At the same time, several prominent organizations (the American College of Physicians, American Academy of Family Medicine, US Preventive Task Force, Canadian Task Force) did not recommend screening mammography for women in their 40s because of the lack of evidence showing that mammography lowers breast cancer mortality among these women.

In February 1993, the NCI convened an international workshop to reassess whether more recent screening mammography trials demonstrated the efficacy of mammography among women 40 to 49 years old. Based on this workshop, the NCI withdrew its recommendation for screening women in their 40s since there was still no scientific evidence that screening mammography decreases breast cancer mortality among these women [1]. Instead, the NCI advised women in their 40s to discuss with their physician the risks and potential benefits of screening mammography.

At present, many scientific organizations and most countries in the world who conduct screening mammography do not recommend screening mammography for younger women, but there are still groups in the United States that advocate such screening (Table 1). This disagreement among organizations may be due, in part, to differences in requirements for recommending screening. Organizations that do not recommend screening mammography among women in their 40s maintain that the goal of screening mammography is to reduce the number of deaths from breast cancer. They further argue that proof that mammography can detect small breast tumors is insufficient grounds for recommending routine screening in this age group. Rather, there must be scientific evidence to show that detection of breast cancer by mammography reduces breast cancer mortality before making such a recommendation.

Data From Randomized Controlled Trials

Randomized controlled trials are the most unbiased means to assess whether a screening test reduces the likelihood of death in a person who has the disease, and thus, are considered the gold standard when evaluating the efficacy of a screening test. Table 2 summarizes data from eight
randomized screening mammography trials. Among women 40 to 49 years old, four of the eight trials reported a nonsignificant increase in breast cancer mortality after 7 to 9 years from the initiation of screening, whereas four found a nonsignificant decrease, indicating a lack of statistically significant benefit or harm from screening mammography. This is in contrast to the data for women age 50 and older, which showed a reduction in breast cancer mortality among all studies (Table 3). Several meta-analyses have combined data from the randomized controlled trials in order to quantify the overall impact of screening mammography among women 40 to 49 years old. The first meta-analysis by Elwood et al of published data from six of the randomized controlled trials of screening mammography found no reduction in breast cancer mortality in women 40 to 49 years old after 7 years from the initiation of screening [2]. A more recent meta-analysis, which combined data from all eight randomized controlled screening mammography trials, revealed a nonsignificant, 2% increase in breast cancer mortality after 7 to 9 years from the initiation of screening [3]. After 10 to 12 years from the initiation of screening, combined results showed a nonsignificant, 17% (95% confidence interval, -35% to +6%) reduction in breast cancer mortality [3].

Pooled data from the five Swedish trials and results from the HIP trial have also suggested a benefit from screening mammography in younger women that does not occur until after 10 years from the initiation of screening [4-6]. A meta-analysis by Smart et al [7] eliminated the Canadian data [8] and included unpublished results from the Gothenborg and two-county Swedish trials. This meta-analysis contained several errors [9]; when these errors were taken into account, the meta-analysis yielded results similar to those previously published [5], that is, that there is a delayed benefit, although statistically not significant, of screening mammography in younger women.

What Accounts for the Discrepancy in Screening Efficacy by Age?

It is unclear why the efficacy of screening mammography in women age 40 to 49 years varies with the length of time from the initiation of screening. The findings are most consistent with two possible explanations:

1. The reduction in breast cancer mortality noted after 10 to 12 years from the initiation of screening occurs because, in women who start screening between 40 and 49 years old, breast cancer is diagnosed when the women are 50 years or older, an age at which mammography is known to be efficacious.
2. A proportion of indolent tumors, if detected early among women in their 40s, will result in a delayed reduction in breast cancer mortality.

Continuation of Screening After Age 50--In the HIP study, 85% of breast cancers in women who started screening between 40 and 49 years old were diagnosed between ages 45 and 54, when most women would have become menopausal [10]. Likewise, the majority of women in the Edinburgh and Malmo trials, which also showed a trend toward a delayed benefit of mammography after 10 to 12 years from the initiation of screening, were also probably age 50 or older and postmenopausal when their breast cancer was diagnosed, since the youngest age of women at the start of screening was 45 years old [11,12]. Computer modeling of the Swedish breast cancer screening trial data estimated that most (70%) of the small observed decrease in breast cancer mortality for women 40 to 49 years old at trial entry may be attributable to the continuation of screening after women reach 50 years of age [13].

Differences in Tumor "Aggressiveness"--An alternative explanation for the variation in efficacy of screening mammography with the length of time from the initiation of screening is possible if one accepts the premise that breast cancer is a heterogeneous disease with two basic forms: a "less aggressive" form that mammography detects in time for treatment to be effective and a second form that is more rapidly fatal regardless of early mammographic detection. In women 40 to 49 years old, mammography may detect some less aggressive tumors that are more curable than similar tumors detected clinically, but because they are less aggressive, a reduction in breast cancer mortality among screened women is delayed for up to 10 to 12 years. If this is true, the reduction in mortality among screened women age 50 and older, who tend to have slower tumor growth rates [14], should also be delayed for 10 to 12 years. Yet, mammography reduces breast cancer mortality by about 25% after only 5 to 6 years from the initiation of screening in older women. This finding suggests that, in women age 50 and older, mammography is able to detect "more aggressive" tumors, since a significant reduction in breast cancer mortality among screened women occurs after only 5 to 6 years from the initiation of screening. It further suggests that mammography detects a substantial proportion of less aggressive tumors, since the cumulative reduction in breast
cancer mortality increases over time. However, among women 40 to 49 years of age, the proportion of less aggressive tumors detected by mammography is small, which may account for the marginal, delayed reduction in breast cancer mortality among screened women. This hypothesis is supported by the observation that a greater proportion of small, screening-detected tumors are associated with positive lymph nodes among women 40 to 49 years old when compared to similar screening-detected tumors in older women [15].

**Summary of Meta-analysis Results**—In summary, based on the results of meta-analyses, there is no reduction in breast cancer mortality among women 40 to 49 years old who undergo screening mammography for 7 to 9 years. It is important to emphasize that if screening mammography is effective in reducing breast cancer deaths among women age 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 age 50 and older. Furthermore, since it is appears that, among women who start screening in their 40s, the majority of breast cancers are detected by mammography after they reach age 50 or older or become menopausal, it may be possible to wait to begin screening then and achieve the same mortality benefit as would occur if screening were started at age 40.

**Are the Data from Randomized Controlled Trials Conclusive?**
Some researchers have argued that it is inappropriate to pool data from several studies to evaluate the efficacy of screening mammography among women 40 to 49 years old, and that such subgroup analyses are inappropriate when initial screening trials were designed for women 40 to 74 years old [16]. However, this is exactly the purpose of a meta-analysis; namely, to combine data from several trials when the number of subjects in any one trial is insufficient to draw a meaningful conclusion [17,18].

Others have argued that the randomized controlled trials of screening mammography are methodologically flawed and should not be used to conclude that mammography lacks benefit in women 40 to 49 years old. However, results from these same trials are used to support the value of screening mammography in women age 50 and older.

Screening mammography trials also have been criticized for using obsolete technology, with the implication that modern mammography is better able to detect breast cancer in younger women. Of note, however, modern mammography has yet to demonstrate improved sensitivity among younger women. In fact, several published studies show that, despite improvements in technology, the sensitivity of modern mammography is still lower for women under age 50 than for women 50 years of age and older [19-23].

Lastly, proponents of screening mammography contend that randomized controlled trials have enrolled too few women to demonstrate a statistical significant benefit among younger women. Yet, if the explanation were simply lack of statistical power, the percentage reduction in breast cancer mortality observed at 7 to 9 years from the initiation of screening (+2%) should be similar to that reported at 10 to 12 years (-17%) but with wider confidence intervals around the point estimate. However, this is not the case.

The argument that too few women have been enrolled to demonstrate a statistically significant benefit from screening mammography also underscores the fact that breast cancer is not common in younger women. Because of this fact, it has been estimated that 1 million women 40 to 49 years old would have to be enrolled in a randomized controlled trial in order to determine with certainty whether or not screening mammography decreases breast cancer deaths in this age group.

**Potential Benefits of Screening**

**Absolute Benefit**
To better understand the potential benefits of screening mammography, it is important to convert the relative risk reduction in breast cancer mortality observed in randomized trials to an absolute reduction in breast cancer deaths. For example, a 50-year-old woman's chance of dying from breast cancer over the next 15 to 20 years is 13 per 1,000 women. Assuming that regular screening mammography reduces breast cancer mortality by 30%, undergoing regular screening mammography reduces this chance to 0.9%, or 9 per 1,000 women (ie, 4 fewer women will ultimately die of breast cancer for every 1,000 women age 50 years who are screened for 10 years) [24].

Because the risk of dying from breast cancer is lower for a woman in her 40s (8 per 1,000 women), the potential absolute risk reduction will be less even if the relative benefit from mammography is the same as in older women (ie, a maximum of 1 to 2 fewer deaths per 1,000 women screened).
However, given that the reduction in breast cancer mortality observed in randomized controlled trials is lower among women 40 to 49 years old, the potential absolute reduction in breast cancer mortality is probably even lower (1 fewer death per 5,000 to 10,000 women screened). Therefore, even if there is some reduction in breast cancer mortality among women age 40 to 49 years who undergo regular screening mammography, the absolute risk reduction will be small because both the incidence and risk of death from breast cancer are low among these women (Figure 1).

**Detection of Small Tumors**

Detection of tumors when they are small improves the cosmetic results of surgery and decreases the morbidity of surgery, regardless of the extent of lymph node involvement. It is unclear whether quality of life is improved by detecting small tumors via mammography since the majority of women still receive adjuvant chemotherapy regardless of tumor size and nodal status.

**Risks of Screening**

**Additional Views, Biopsies**

When abnormalities are detected on screening mammography, women are recalled for further diagnostic tests, which may include additional mammographic views, ultrasound, or clinical breast examination. Biopsy is subsequently recommended in some of these women after additional tests. Although the proportion of women recalled is similar across all ages, the likelihood of a false-positive examination is higher among women under age 50 years because the incidence of breast cancer is low in these women. Kerlikowske et al have demonstrated this by determining the positive predictive value of a screening mammography by age. They have shown that the positive predictive value of mammography increases with age and is highest among those at greatest risk for disease; ie, women age 50 and older and those with a family history of breast cancer (Table 4). Compared with women age 50 and older, women under age 50 underwent 2.5 times more biopsies and 3 times as many diagnostic procedures to diagnose one-fifth as many cancers [25]. Some do not consider additional diagnostic procedures, including breast biopsy, to be harmful, but the experience and trauma of having a biopsy can result in anxiety that persists for up to 18 months, even after women are told they do not have breast cancer [26-29]. Although the risk is small, there are complications associated with breast biopsies, such as hematomas, infection, and scarring. The infection rate for biopsies of lesions when there is no periductal mastitis is 2% [30]. Complications from the wire localization itself include vasovagal reactions (7%) and, rarely, prolonged bleeding (1%) and extreme pain (1%) [31].

In addition, some women may be labeled as a result of having an abnormal mammographic examination, which may affect subsequent screening and insurance status, as well as compliance. How much "human cost" (ie, anxiety, labeling, morbidity from procedures, inconvenience) results from a false-positive examination is unknown. However, since the proportion of women in the population who are between 40 and 49 years old is large (Figure 2), this will magnify any costs, both human and economic, of screening younger women.

**Ductal Carcinoma in Situ**

Since the initiation of widespread screening mammography in the mid-1980s, there has been a 200% increase in preinvasive cancer, or ductal carcinoma in situ (DCIS), among women of all ages [32-33]. In some screening programs, up to 50% of mammographically detected cancers in women under age 50 are DCIS [25,34]. It is important to point out that DCIS may be more common than we realize; one autopsy study demonstrated that 20% to 25% of women over the age of 35 have DCIS [35]. Therefore, it is likely that a significant cohort of women will have DCIS detected that might never have come to medical attention or become clinically significant if they had not undergone screening mammography.

Numerous studies have shown that only 15% to 25% of DCIS lesions progress to invasive cancer over 5 to 10 years [36-40], and the progression rate may be as low as 7% [41]. Several studies have suggested that the histology of DCIS lesions may be important and that a higher proportion (11% to 30%) of high-grade, comedo lesions progressing to invasive cancer over 5 to 10 years, whereas low-grade noncomedo lesions have a very low progression rate (5%) [39,42]. Despite this evidence, there is a tendency to treat all histologic types of DCIS with either mastectomy or lumpectomy and radiotherapy to prevent progression of the few DCIS cases that have the potential to progress to invasive cancer [32]. It has been estimated that in 1992, approximately 23,000 cases of DCIS were diagnosed in the US and that 10,000 were treated by mastectomy [33]. The aggressive treatment of DCIS lesions illustrates that once the possibility of progression to invasive cancer is raised, it is difficult for clinicians and patients alike to opt for watchful waiting.
No randomized clinical trial has demonstrated a decrease in breast cancer mortality among women with DCIS who are treated with lumpectomy, either alone or with radiotherapy. What is known from the National Surgical Adjuvant Breast Project (NSABP) B-17 trial, which randomized women with DCIS to receive either lumpectomy or lumpectomy plus radiotherapy, is that the addition of radiation can decrease the rate of recurrence of invasive disease from 10.5% to 2.9% in the first 5 years after treatment [38]. This trial will eventually be able to determine whether the addition of radiotherapy affects breast cancer mortality or, in fact, whether it prevents progression to invasive cancer over the long term. No studies are underway to evaluate the impact of surveillance vs surgical treatment of DCIS on breast cancer mortality.

**Ignoring a Palpable Lump**
The Canadian National Breast Screening Study is the only randomized controlled trial designed exclusively to determine the efficacy of screening mammography in women 40 to 49 years of age [8,43]. The screening program, which used two-view mammography and clinical breast examination, reported one of the highest sensitivities for a breast cancer screening modality of any randomized clinical trial [1]. Nevertheless, this trial showed a nonsignificant increase in breast cancer mortality after 7 years from the initiation of screening. As mentioned above, other clinical trials have also found a nonsignificant increase in breast cancer mortality in the screened group after 5 to 7 years from the initiation of screening (Table 2).

One possible explanation for this finding is that women may delay seeking medical attention when they find breast lumps if they have had a recent normal mammographic examination. A delay in evaluating breast lumps may postpone the diagnosis of breast cancer and result in a higher, less curable stage of disease. For this reason, women in their 40s who choose to undergo screening mammography should be informed that a normal examination does not rule out the possibility of breast cancer. Furthermore, women who subsequently develop breast symptoms after a normal mammographic examination should not be falsely reassured that they do not have breast cancer and should be promptly be evaluated by their primary-care physician.

**Economic Costs**
*Figure 2* demonstrates that, compared with women 50 years and older, many more young women will have to be screened to detect existing breast cancers. Thus, even if the specificity of mammography is the same for younger and older women, the absolute numbers of false-positive results will be higher in younger women because many more women without breast cancer will undergo screening. If, indeed, the specificity of mammography is lower in younger women, the problem of false-positives will be magnified.

Proponents of screening younger women have argued that the motivation behind the NCI's decision to recommend against screening women under age 50 was based on the desire to reduce costs at the expense of the potential benefit to a given individual. Although that decision was based on evidence from randomized screening mammography trials, not on a cost analysis [1], such criticisms imply that it is wrong to consider cost.

The annual cost of screening mammography in the United States, if 40% of the population is screened, has been estimated to be around 3 billion dollars [44]. Moreover, it is likely that the majority of women being screened are young women [25], for whom the efficacy data are controversial, while older women continue to be underscreened [45]. Since the pool of resources for health care is not infinite, clinical scientists and physicians must identify and recommend screening interventions for those populations that have the greatest potential benefit relative to other treatments and screening interventions.

**Women With a Family History of Breast Cancer**
Although several organizations recommend screening mammography for women age 40 to 49 years who are at high risk for breast cancer (those with a first-degree relative [mother, sister, or daughter] with breast cancer), there is no evidence that regular screening mammography reduces the risk of death from breast cancer among these women. A recommendation to screen younger women at high risk of breast cancer has been established primarily because of the increased burden of suffering. Women 40 to 49 years old with a first-degree relative with breast cancer have a risk of breast cancer similar to that of women age 50 to 59 years without a family history. The higher prevalence of breast cancer among women 40 to 49 years old with a family history of breast cancer results in a higher positive predictive value for screening mammography and, consequently, fewer unnecessary diagnostic work-ups when mammography is abnormal [25]. However, the sensitivity of mammography may be lower among younger women with a family history of breast cancer, compared to those who do not have a family history (K. M. Kerlikowske, MD, personal communication, September 1995), which may influence the potential benefits of screening.
mammography among these women. Since it is unknown whether screening mammography reduces breast cancer mortality among women age 40 to 49 years with a family history of breast cancer, it is important that these women and their physicians understand these limitations before opting for screening mammography.

**Conclusions**

Among women 40 to 49 years old, there is no evidence to show that screening mammography decreases breast cancer mortality for the first 7 to 9 years of screening. However, there may be a small delayed benefit after 10 to 12 years from the initiation of screening. Nevertheless, even if there is a small delayed reduction in breast cancer deaths, the absolute benefit will be small because the incidence of breast cancer is low in young women.

The costs per breast cancer detected among younger women will be higher compared to older women because screening will more likely result in a false-positive examination and, consequently, more diagnostic evaluations, to be around 3 billion including breast biopsies. Also, a high proportion of breast cancer detected among younger women is DCIS, which, for the most part, is not likely to be clinically significant. Consequently, screening mammography may result in a significant proportion of younger women undergoing unnecessary breast surgery and radiation.

When the benefits of an intervention are unclear, physicians should involve women in the decision and discuss its risks and benefits. For women 40 to 49 years old, even those with a family history of breast cancer, the potential benefits and risks of screening should be discussed. If women age 40 to 49 years choose or are offered regular screening mammography, the biology of the disease in these women suggests that any potential benefit will be optimized if they undergo annual screening [46]. Clearly, our primary focus should be on designing efficient, effective programs for screening women age 50 to 70 years. There is good scientific evidence that screening mammography decreases breast cancer mortality among these women, who, therefore, are likely to derive the greatest benefit from screening.

**References:**


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