

## CLINICAL DECISIONS

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## Mammography Screening for Breast Cancer

*This interactive feature addresses the approach to a clinical issue. A case vignette is followed by specific options, none of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options. Readers can participate in forming community opinion by choosing one of the options and, if they like, providing their reasons.*

## CASE VIGNETTE

A 40-year-old woman presents to her primary care physician for a routine health maintenance examination. Overall, she has been feeling well. She takes no medications. She lives with her husband and their two children, who are 7 and 11 years of age. She underwent menarche at the age of 12. Before the birth of her first child, she took combined oral contraceptives for 6 years. She breast-fed each of her children for approximately 1 year. For the past 4 years, she has used a levonorgestrel intrauterine device for contraception. She works as an accountant and exercises on the weekends. Her diet includes regular consumption of fish, chicken, and vegetables, and she eats red meat once a week. She does not smoke, and she consumes an average of four glasses of wine each week. Her family history is notable for prostate cancer in her father that was diagnosed when he was 75 years of age and hypertension in her mother that was diagnosed when she was 60 years of age. There is no history of colon cancer, lung cancer, or breast cancer among her parents or grandparents. She undergoes a complete physical examination, including a clinical breast examination. All findings are normal. She has never undergone mammography, and she asks her primary care physician about recommendations regarding mammography screening.

Which one of the following approaches do you find appropriate for women who, like the woman in the vignette, are at average risk? Base your choice on the published literature, your own experience, recent guidelines, and other sources of information, as appropriate.

1. Recommend screening mammography starting at the age of 40.
2. Recommend screening mammography starting at the age of 50.
3. Do not recommend screening mammography.

## OPTION 1

## Recommend Screening Mammography Starting at the Age of 40

Robert A. Smith, Ph.D.

At what age should women begin breast-cancer screening, and what information can women and their clinicians use to help inform this decision? One school of thought asserts that progress in therapy has eclipsed the benefit of early detection and that harms associated with screening are excessive and outweigh the benefits.<sup>1,2</sup> There is substantial evidence to the contrary,<sup>3</sup> however, and the methodologic flaws that lead to these claims have been clearly identified.<sup>4,5</sup>

Another school of thought discourages initiation of screening until the age of 50, emphasizing that the 10-year risk of breast cancer is lower when a woman is in her 40s than when she is in her 50s (1 case among 69 women vs. 1 among 42), that mammography reduces the risk of death from breast cancer by only 15%, that 1904 women 40 to 49 years of age need to be invited to be screened over a period of 11 to 20 years to save one life, and that the harms, principally false positive findings, are considerable.<sup>6</sup>

A third school of thought — one that supports screening starting at the age of 40 — is more compelling. Our ability to predict population risk is reasonably accurate, yet we are not able to tell a woman with confidence that it is safe to postpone — not probably safe to postpone — beginning screening until the age of 50. Furthermore, 73.6% of non-Hispanic white women in their 40s have an absolute risk of breast cancer that is greater than that of a 50-year-old woman without risk factors.<sup>7</sup> In addition, one in six breast-cancer deaths is attributable to a diagno-

sis that was made when the woman was in her 40s, and breast cancer is a leading cause of premature death among women; one third of all the years of life lost as a result of breast cancer are due to diagnoses that were made when the women were in their 40s.<sup>8</sup> Breast cancer among women in their 40s is a considerable, not small, fraction of the overall burden of this disease.

Although a meta-analysis of randomized, controlled trials showed a 15% reduction in mortality among women randomly assigned to be invited to undergo screening mammography in their 40s,<sup>6</sup> individual randomized, controlled trials and recent evaluations of modern mammography screening have shown substantially greater reductions in mortality. Consider the recent Swedish study showing that among women who underwent screening, there were 29% fewer deaths from breast cancer after 16 years in counties that offered mammography than in those that did not.<sup>3</sup> The estimate that 1904 women 39 to 49 years of age need to be invited to be screened to save one life is an imprecise and nebulous surrogate for the number needed to screen because it is influenced by deaths among women in the invited group who did not undergo screening and by variable follow-up periods (ranging from 11 to 20 years) in the individual studies. In contrast, on the basis of direct observation of women 39 to 49 years of age who actually underwent screening mammography over a 7-year period and were followed for 20 years, the number needed to screen was 726<sup>9</sup> — a number that is less even than the estimated number needed to invite (1339) for women in their 50s.<sup>6</sup>

What about harms? The risk of a false positive finding is greater than 50% during a decade of regular screening,<sup>10</sup> and false positives are associated with temporary anxiety.<sup>6</sup> Nevertheless, women have reported that they accept the trade-off of false positives in favor of finding breast cancer early.<sup>11</sup> Estimates of overdiagnosis have ranged from 0 to more than 50%, but the rates are small (<10%) in studies that properly adjust for lead time and trends in incidence.<sup>12</sup> We should also consider the harms associated with electing not to be screened before the age of 50. A recent case series showed that women whose breast cancer was not diagnosed by mammography were more likely to be diagnosed with a stage II or higher tumor than were women in

whom breast cancer was diagnosed by mammography (66% vs. 27%) and were more likely to have a mastectomy (47% vs. 25%); undergo surgery, radiation therapy, and chemotherapy (59% vs. 31%); and have poorer 5-year survival rates.<sup>13</sup>

Screening can be thought of as a kind of insurance. As with all insurance, there are costs for protection against adverse events that have a low probability of occurrence but could be catastrophic if they occurred without the insurance.<sup>14</sup> In that context, given the evidence, there are good reasons to begin screening at the age of 40.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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## OPTION 2

# Recommend Screening Mammography Starting at the Age of 50

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and Diana L. Miglioretti, Ph.D.

When evidence-based guidelines for breast-cancer screening are developed, the primary consideration is whether the benefits outweigh the harms. The benefits of screening mammography include breast-cancer deaths averted and life-years gained by the detection of biologically significant cancers before they become apparent clinically. The harms of screening healthy women include false positive tests, radiation exposure from screening and follow-up imaging, invasive follow-up procedures, and overdiagnosis. The balance of benefits and harms is tipped to favor more benefit than harm if screening mammography is routinely offered to average-risk women starting at 50 years of age.

High-quality evidence is available from randomized, controlled trials and from U.S. population-based simulation models, and the two sources show similar findings regarding screening mammography.<sup>15,16</sup> Among women 50 to 74 years of age screened every 2 years, 12 rounds of screening 1000 women result in 7.5 breast-cancer deaths averted, 121 life-years gained, and 940

false positive mammography results requiring diagnostic imaging leading to 66 false positive biopsy results. By comparison, if 1000 women start screening at 40 years of age and are screened every 2 years, 5 more screening rounds would result in an additional 0.7 breast-cancer deaths averted, 21 life-years gained, 4921 mammograms performed, and 470 false positive mammography results requiring diagnostic imaging leading to 33 false positive biopsy results. The ratio of benefit to harm with screening mammography is more favorable among women 50 to 74 years of age than among younger women because mammography is less accurate in younger women, and the low incidence of disease results in a higher rate of false positive results and a lower rate of breast-cancer deaths averted. Furthermore, increasing the frequency of screening from every 2 years to every year almost doubles the harms,<sup>10</sup> without increasing the benefit.

As now reported in the *Journal*, Bleyer and Welch<sup>1</sup> suggest that the benefits of screening mammography are modest and raise the question of whether the effectiveness can be improved. One approach is to target women who are at an increased risk for breast cancer and advanced-stage disease, because their tumors are more likely to become metastatic and fatal, and thus are more likely to benefit from earlier diagnosis. Factors that increase the risk of breast cancer and advanced stage at diagnosis include high breast density, use of postmenopausal estrogen plus progestin for 5 or more years, and postmenopausal obesity.<sup>17,18</sup> Risk-based screening could also decrease the potential harms by identifying women at low risk for breast cancer who could begin screening at a later age and be screened less often, such as women with fatty breast density.<sup>19</sup>

Given this evidence, we agree with the U.S. Preventive Services Task Force and with most countries with breast-cancer screening programs, which recommend that women undergo screening mammography every 2 years beginning at the age of 50. Average-risk women 40 to 49 years of age, for whom the benefits of screening are small and the potential for harms great, should be given the opportunity to make an informed decision about screening by being made aware of the potential benefits of mammography (1 death from breast cancer averted for every

1430 to 1900 women invited to be screened for 10 years),<sup>15,16</sup> their chances of having a false positive mammography result and of having a false positive breast biopsy result (42% and 5%, respectively, after 5 biennial screening rounds and 61% and 7%, respectively, after 10 annual screening rounds),<sup>10</sup> and their chances of overdiagnosis and overtreatment. Targeting screening to women 40 to 49 years of age with combinations of risk factors that increase the risk of breast cancer by a factor of 2 to 4, such as high breast density, a family history of breast cancer, or a history of breast biopsy, would maximize the benefit and limit the harms of screening in this group.<sup>19,20</sup> Women at the highest risk for breast cancer, such as those who carry the BRCA1 or BRCA2 mutation, should undergo breast magnetic resonance imaging and mammography before the age of 40.

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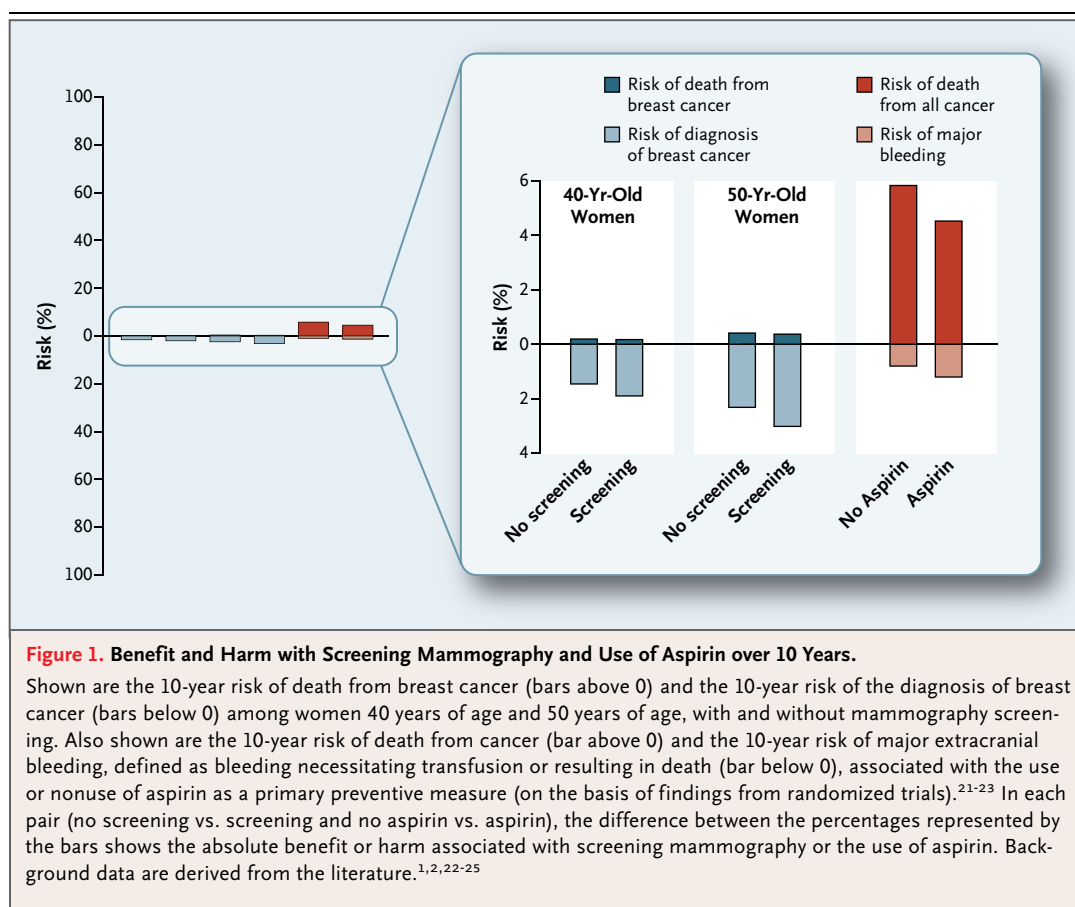
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### OPTION 3

## Do Not Recommend Screening Mammography

Mette Kalager, M.D., Ph.D.

The small absolute benefit of screening for 40-year-old women has been known for years. Of greater concern is that the harms are greater than previously anticipated and may outweigh the benefits. The most harmful side effect of screening is overdiagnosis, which results in unnecessary treatment, including surgery, radiation, hormonal treatment, and chemotherapy. As Bleyer and Welch now convincingly show in the *Journal*, as many as 31% of all breast cancers in the United States are overdiagnosed.<sup>1</sup> The 10-year risk of breast cancer (including overdiagnosis) for a 40-year-old woman is 1.90%.<sup>21</sup> The corresponding risk without screening would be 1.46%. Thus, 0.44% of 40-year-old U.S. women are harmed by screening mammography — 10 to 20 times as



many as those who benefit from screening mammography as a result of reduced mortality. Furthermore, the balance of benefits and harms for 50-year-old women is similar to that for 40-year-old women (Fig. 1). On the basis of the small absolute benefit and the substantial harms, I do not currently recommend screening mammography for average-risk women of any age.

More than 600,000 women were enrolled in several randomized trials of mammography screening more than 30 years ago. The trials showed a reduction in breast-cancer mortality but no effect on all-cause mortality. In recent decades, breast-cancer treatment has improved greatly, resulting in reduced mortality even among women with advanced disease. Thus, the reduction in mortality from mammography screening may be significantly smaller today than when the trials were performed.

What is the absolute benefit of breast-cancer screening for a 40-year-old woman? First of all,

the 10-year risk of dying from breast cancer for a 40-year-old woman is low (0.17%).<sup>21</sup> There is heated debate on whether screening reduces breast-cancer death by 25% (as observed in the early randomized trials) or 10% (as observed in more recent studies<sup>2,24,25</sup>); however, the difference is not clinically meaningful. A 25% relative reduction results in an absolute benefit of 0.04 percentage points, and a 10% reduction would result in an absolute benefit of 0.02 percentage points.

The benefits of mammography screening are smaller than those of other interventions, such as the use of aspirin to reduce cancer mortality (Fig. 1). The use of aspirin for 5 years, as compared with no use of aspirin, reduced the 10-year risk of death from cancer by 1.3 percentage points but increased the risk of major bleeding by 0.4 percentage points.<sup>22,23</sup> Clearly, the benefits are much smaller and the harms much greater with mammography screening. Would

we discuss aspirin as a preventive measure against cancer death if the effects were smaller than the harms? Probably not.

The decision regarding screening mammography depends on the balance of benefits and harms and the way in which a woman and her physician weigh these competing factors. In my view, the benefits do not exceed the harms. Thus, given the data currently available, I do not recommend mammography screening for average-risk women of any age. I would ask the woman in the vignette to come back when she is 50 years of age. In 10 years, we might have more data to provide a different recommendation for her.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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