The Cost-Effectiveness of Screening Mammography beyond Age 65 Years: A Systematic Review for the U.S. Preventive Services Task Force

Jeanne Mandelblatt, MD, MPH; Somnath Saha, MD, MPH; Steven Teutsch, MD, MPH; Tom Hoerger, PhD; Albert L. Siu, MD, MSPH; David Atkins, MD, MPH; Jonathan Klein, MD; and Mark Helfand, MD, MS, for the Cost Work Group of the U.S. Preventive Services Task Force

Purpose: There are few data on the effects of disease biology and competing mortality on the effectiveness of screening women for breast cancer after age 65 years. The authors performed a review to determine the costs and benefits of mammography screening after age 65 years.


Study Selection: Studies were identified by using MEDLINE and the National Health Service Economic Evaluation Database. The authors included research on screening after age 65 years conducted from a societal or government perspective; reviews and analyses of other technologies were excluded.

Data Synthesis: 115 studies were identified and 10 met inclusion criteria. One study modeled age-dependent assumptions of disease biology. No study fully captured the potential harms of screening, including anxiety associated with false-positive results, overdiagnosis, and previous knowledge of cancer or living longer with the consequences of treatment. Studies differed in the specific strategies compared and in analytic approaches. On average, extending biennial screening to age 75 or 80 years was estimated to cost $34,000 to $88,000 (2002 U.S. dollars) per life-year gained, compared with stopping screening at age 65 years. Two studies suggested that it was more cost-effective to target healthy women than those with several competing risks for death.

Conclusions: Current estimates suggest that biennial breast cancer screening after age 65 years reduces mortality at reasonable costs for women without clinically significant comorbid conditions. More data are needed on disease biology and preferences for benefits and harms in older women.


For author affiliations, see end of text.
tify cost-effectiveness analyses. For our MEDLINE search, we added the exploded MeSH term cost–benefit analysis. In the National Health Service Economic Evaluation Database, we limited the search to economic evaluations. We chose 1989 as a starting point because it marked the time period in which papers on cost-effectiveness of breast cancer screening began to appear. To identify studies not captured by our database searches, we manually searched the reference lists of retrieved articles and contacted selected authors and experts in the field to identify additional studies.

Two investigators independently reviewed each identified abstract, and potentially eligible articles were retrieved. Using information in the abstracts, we excluded studies that were not cost–utility analyses or cost-effectiveness analyses, such as economic evaluations that did not quantify the health outcomes achieved for a given cost. We also excluded studies that reported only cost per patient screened or cost per type of cancer detected; studies without original analyses; studies that did not allow assessment of screening after age 65 years; and studies that were not performed from a societal perspective or the perspective of a third-party payer, such as Medicare or a national health system. When several publications reported results from the same cost-effectiveness model, we included more than 1 study if the studies contained different information. If several articles presented the same analyses, we selected the most comprehensive analysis and used the other articles for supplemental information. When the decision about whether to include a study was unclear from the title and abstract, we evaluated the full article. A 4-member working group reached consensus on final inclusion or exclusion of articles. Excluded studies are summarized in an appendix that is available from the authors.

One reviewer extracted data into evidence tables. Other members checked the results, and discrepancies were resolved by consensus. Data were abstracted on the basis of a modeling approach; screening intervals; the assumptions of each study about the epidemiology and natural history of breast cancer; estimates of variables related to the effectiveness of screening, including test accuracy, adherence rates, and complication rates; estimates of the costs of screening, diagnosis, and treatment; the proportion of types of cancer and cancer deaths prevented by screening; and the effect of varying key parameters (sensitivity analyses).

For each study, we tabulated life-years gained and costs per person for different age groups. The evaluated strategies were ordered by effectiveness. Costs were updated to 2002 U.S. dollars by using the Consumer Price Index for medical care (29). Incremental cost-effectiveness ratios were then calculated, comparing screening after 65 years of age to screening cessation at 65 years of age.

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RESULTS

Our initial searches identified 115 potentially relevant studies. Ten studies met our inclusion criteria and included specific data on the cost-effectiveness of screening older women (10, 22, 25–27, 30–34). The most common reasons for excluding the remaining articles were lack of data on screening after 65 years of age, study type other than a cost-effectiveness study, and duplicate publication.

The Table shows the basic features of the 10 included studies. All were cost-effectiveness analyses with benefits expressed in life-days or life-years gained and costs expressed in U.S. (or other) dollars. Most studies expressed incremental results for extending screening to ages 75 or 80 years, compared with ceasing screening at age 65 years. Two studies presented results as an average for screening from ages 50 to 74 or 79 years (25, 34). Each study considered the direct costs of care, including the costs of screening, diagnostic tests, and treatment. No study considered patient time costs associated with screening, diagnostic, or surveillance procedures or treatment of cancer. All studies discounted costs and effects. Discount rates varied from 3% to 6%; the most common rate was 5%. The variables used in the different studies were similar to those noted in the U.S. Preventive Services Task Force summary of recommendations (35).

Overall, despite methodologic differences, the cost-effectiveness results were fairly consistent. The results for biennial screening after age 65 years generally indicated incremental costs of approximately $34,000 to $88,000 (2002 U.S. dollars) per life-year saved compared with stopping screening at age 65 years (Table); costs per life-year saved increased after age 65 years. It was also cost-effective to screen women after age 65 years if they had not been regularly screened before age 65 years (27, 32).

Most studies considered the average risk for breast cancer, but 1 study specifically tested results by level of risk for breast cancer (based on bone mineral density and a proxy for lifetime estrogen exposure) (27). One study presented results separately for older black and white women (32), since black women have historically had lower screening rates and higher mortality rates than white women (1, 36). The remaining analyses explored results for women at average risk for breast cancer on the basis of population incidence and mortality rates.

A key issue in evaluating the benefits of screening older women is that in this group, in addition to an increased risk for breast cancer, the probability of developing other illnesses that can decrease life expectancy is also higher, offsetting survival benefits of early cancer detection. For example, if a woman has a small breast tumor detected at screening but dies of a myocardial infarction the next year, screening had no benefit in extending life expectancy.
Two papers in our review specifically addressed the effect of comorbid conditions on screening decisions (30, 32). One paper considered the situation for women with dementia (30), and the other assessed the influence of congestive heart failure and hypertension (32). These studies found that screening reduces breast cancer mortality in all but the sickest women. The remaining studies captured the effects of average numbers of comorbid conditions through use of general population mortality rates.

Detecting cases of cancer or ductal carcinoma in situ that would not have become clinically evident or would not have progressed to invasive disease before death might be considered a screening-related harm or overdiagnosis. Depending on a woman’s preference, living for a longer period with the diagnosis of breast cancer and the consequences of treatment (such as scars and diminished arm mobility) can reduce quality of life, especially in cases where early detection and treatment do not extend life because of competing forces of mortality. These harms are not explicitly modeled in any study in our review, and no study considered ductal carcinoma in situ separately or made any assumptions about overdiagnosis. Two studies attempted to capture negative consequences of screening through quality adjustment of a woman’s remaining years of life after diagnosis of cancer (27, 32). However, the valuation of the quality of this time (that is, utility or preference value) was based on expert opinion, not directly on patients with cancer or general populations of women (19). Screening may also harm women who have a positive mammography result but do not have cancer. One study incorporated the short-term disutility from anxiety and discomfort associated with a false-positive screening result and found that it did not alter the conclusions of the analysis (32). The harms of operative mortality among women receiving treatment for breast cancer was explicitly incorporated in only 2 studies (30, 32) but was low enough (<2%) not to affect conclusions. Thus, in the studies included in this review, potential harms have been modeled incompletely.

If breast cancer is a slower-growing neoplasm in older women than in younger women, then screening at intervals longer than 1 year may be a cost-effective option. Most base-case analyses examined biennial screening intervals. The analysis by Mandelblatt and colleagues (32) considered a one-point-in-time screening decision, and the model by Eddy (26) included annual screening for a 10-year period. Rosenquist and Lindfors (25, 34) compared combinations of more frequent screening for younger women and longer screening intervals for older women. They concluded that the discounted cost-effectiveness of annual screening from ages 40 to 49 years, followed by biannual screening from ages 50 to 79 years, yielded equivalent cost-effectiveness of screening annually from ages 50 to 79 years. However, the authors did not separately test different intervals after age 65 or 70 years. de Koning and colleagues (22) included triennial screening but present the results only for women 50 to 65 years of age, making direct comparisons with other studies difficult.

In general, each model used data on stage-specific survival to simulate natural disease history. Only 2 studies explicitly assumed age-specific disease biology (31, 33). These authors assumed that the preclinical detectable phase increased from 1.8 years at 35 years of age to 2 years at 50 years of age and to 6.2 years at 70 years of age. This assumption should favor screening, since fewer cases will rapidly progress and be missed by screening. However, as noted earlier, this also implies the possibility of longer intervals between screenings as women age. It also implies less virulent disease, leading to lower survival benefits in older women than in younger women. Of note, the 2 studies that modeled age-specific disease behavior and the studies that used observed stage shifts with screening (for example, from regional to distant) came to similar conclusions about screening.

All studies assumed the same mammography test sensitivity for all age groups. Mammography has a higher sensitivity in older women than in younger women (10). Assuming equivalent sensitivity across age groups underestimates effectiveness for older women. In addition, all studies used a single estimate of sensitivity for all rounds of screening. Previous studies have demonstrated that sensitivity is typically greatest in the first round of screening (11). When detection of prevalent (larger) tumors is included with detection of incident (smaller) lesions, sensitivity values are overestimated, biasing results in favor of screening for all age groups.

With 1 exception (22), all analyses assumed that 100% of women attended screening and adhered to diagnosis and treatment. If older women are less likely to adhere to screening than women 65 years of age and younger, then costs will decrease. If the costs decrease in exact proportion to the benefits, then this will not affect conclusions. If either costs or benefits vary disproportionately, the cost-effectiveness ratio can be higher or lower. de Koning and colleagues (22) used the actual age-specific rates of participation seen in the Dutch trials (65% at age 70 years and 45% at ages 71 to 75 years) and found that costs and benefits decreased proportionately with decreasing participation. If older women adhere to screening (and incur screening costs) but do not adhere to prompt diagnosis or recommended treatment, they will not fully benefit from earlier detection, and cost-effectiveness ratios will increase. However, lower adherence could result in lower costs if women not using mammography do not develop breast cancer or die of competing causes before breast cancer surfaces.

Most sensitivity analyses varied 1 parameter at a time (1-way analyses). Parameters that caused cost-effectiveness ratios to vary substantially from the base case in sensitivity analyses included cancer incidence rates (such as a 2-fold increased incidence in women with a family history of breast cancer) (26, 32), differences in assumptions about
mortality reductions (22, 25, 27, 34), quality adjustment (27), and discount rates for the oldest groups of women in poor health (32). Discount rates reflect the fact that most people value present years of life more than future years. If older women value the present over the future to a greater extent than younger women, then screening may seem less

<table>
<thead>
<tr>
<th>Author, Year (Reference)</th>
<th>Time Horizon</th>
<th>Type of Model</th>
<th>Interval</th>
<th>MammoGraphy Effectiveness</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Messecar, 2000 (30)</td>
<td>Lifetime</td>
<td>Markov</td>
<td>Biennially</td>
<td>Based on SEER stage distribution§</td>
<td>95</td>
<td>95</td>
</tr>
<tr>
<td>Rosenquist and Lindfors, 1998 (34)</td>
<td>Age 40–79 y</td>
<td>Markov</td>
<td>Annually for age 40–49 y; biennially for age 50–79 y</td>
<td>39% reduction in mortality with biennial for age ≥ 50 y; 13% for age 40–49 y</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td>Lindfors and Rosenquist, 1995 (25)</td>
<td>Age 40–79 y</td>
<td>Markov</td>
<td>Annually for age 40–49 y; biennially for age 50–79 y</td>
<td>Mortality reduction varies by age; 4%–23% for age 40–49 y; 23%–32% for age 60–79 y</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td>Brown, 1992 (10)</td>
<td>20 y starting at age 50 y</td>
<td>CANTROL Markov process**</td>
<td>Biennially</td>
<td>Observed from RCTs ~30% reduction in mortality</td>
<td>Not stated</td>
<td>98.6</td>
</tr>
<tr>
<td>Boer et al., 1998 (31)</td>
<td>Lifetime</td>
<td>MISCAN</td>
<td>Biennially, examines triennially</td>
<td>Observed from RCTs ~30% reduction in mortality</td>
<td>Varies by lesion size: 40, ductal carcinoma in situ; 65, T1a; 80, T1b; 90, T1c; 95, T2</td>
<td>Not stated</td>
</tr>
<tr>
<td>Boer et al., 1999 (33)</td>
<td>Lifetime</td>
<td>MISCAN</td>
<td>Biennially, examines annually and triennially</td>
<td>Observed from RCTs ~30% reduction in mortality</td>
<td>Same as Boer et al., 1998 (31)</td>
<td>Not stated</td>
</tr>
<tr>
<td>de Koning et al., 1991</td>
<td>1990–2017</td>
<td>MISCAN</td>
<td>Biennially</td>
<td>Observed from RCTs ~30% reduction in mortality</td>
<td>Same as Boer et al., 1998 (31)</td>
<td>Not stated</td>
</tr>
<tr>
<td>Eddy, 1989 (26)</td>
<td>10 y</td>
<td>CANTROL Markov process**</td>
<td>Annually</td>
<td>Unknown</td>
<td>Not stated</td>
<td>98.6</td>
</tr>
<tr>
<td>Kerlikowske et al., 1999</td>
<td>Lifetime</td>
<td>Markov</td>
<td>Biannually</td>
<td>27% reduction in mortality (22%–32%); assume benefits continue for 5 years after cessation of screening</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td>Mandelblatt et al., 1992</td>
<td>Cross section, 1 point in time</td>
<td>Markov</td>
<td>1 point in annual program</td>
<td>Based on SEER stage distributions†</td>
<td>75</td>
<td>90</td>
</tr>
</tbody>
</table>

* HMO = health maintenance organization; MISCAN = microsimulation of cancer (a Monte Carlo simulation approach); NA = not available; RCT = randomized controlled trial; SEER = Surveillance, Epidemiology, and End Results.
† 2002 U.S. dollars based on the Consumer Price Index.
§ Incremental costs per additional life-year, compared with screening until age 65 y, unless otherwise specified.
| Effectiveness based on stage is estimated by comparing stage distribution without screening with more favorable stage distribution with screening.
| Ratio includes annual screening for age 40–49 y, which overestimates results for women older than 50 y of age. Note that results are average results over the age range and do not allow separation of data for extending screening after age 65 y.
¶ Analysis includes annual screening for age 40–64 y, then biennially for age 65–79 y, compared with biennial screening for age 50–59 y, so incremental ratio includes costs of starting earlier and extending screening to age 79 y.
** CANTROL is a computer program to calculate outcomes and costs.
favorable for older women compared with younger women. Kerlikowske and colleagues (27) explicitly tested the effects of increasing the discount rate from 0% to 15% (that is, increasing the preference for present vs. future years). They found that, among women valuing the present versus the future to the greatest degree (discount rate,
15%), nearly 1000 women 69 to 79 years of age would need to be screened to extend life by 1 year per woman. If women valued the future and the present equally (discount rate, 0%), then only 146 women would need to be screened to extend life by 1 year per woman (27). Beyond time preferences, at the lower ranges of life expectancy, the harms of screening outweigh the benefits for women with a life expectancy of less than 5 years (for example, women ≥85 years of age with heart failure) (32). Other parameters had less effect on results.

**DISCUSSION**

The results of this review on cost-effectiveness literature are intended to help make clinical and policy guideline decisions on the optimal use of breast cancer screening for older women. Our review suggests that, over a range of assumptions, it remains cost-effective to screen older women for breast cancer every 2 years according to current medical spending. For instance, the incremental costs of $34 000 to $88 000 per life-year saved for screening beyond age 65 years compared with stopping at age 65 years are roughly similar to the costs of $16 000 to $72 000 (1992 U.S. dollars) per life-year saved associated with monotherapy of mild to moderate hypertension in nonelderly populations (24, 32). However, screening becomes more costly and harms begin to outweigh benefits in the sickest women, such as those with dementia or other comorbid conditions that limit life expectancy to that seen at approximately age 85 years (that is, about 5 years). In addition, screening is cost-effective if the biology of disease is similar to that seen in younger women (that is, if breast cancer is not a more benign disease in older women).

Screening may have a secondary benefit of detecting tumors at early stages to allow less risky operative procedures (such as lumpectomy under local anesthesia compared with mastectomy under general anesthesia) and adjuvant therapies (such as tamoxifen vs. multidrug chemotherapy). We know little about how older women approach decisions about treatment. Of interest, in studies of older women, women’s preferences about postoperative quality of life affected their choice of initial breast cancer treatment (37). In 1 study, older women with cancer detected by screening were more likely to feel that they had a greater choice of treatment (breast conservation vs. mastectomy) than women with clinically detected cancer; older women choose breast-sparing surgery more often than mastectomy (38). Larger studies are needed to determine whether having cancer detected by mammography actually increases the proportion of older women undergoing breast conservation versus mastectomy. Currently, there are insufficient data to estimate the potential benefit of breast cancer screening for women who would have received a clinical diagnosis at a later date, when they would have fewer treatment options. Additional data on preferences about quality of life after treatment for ductal carcinoma in situ and invasive lesions are also needed before we conclude that the benefits of screening outweigh the harms. New adjuvant therapy, such as aromatase inhibitors, could also change the overall cost-effectiveness of early detection and treatment through their noncancer health effects (for example, improving bone density and reducing deaths associated with hip fractures).

Assumptions about disease biology have important implications for devising optimal screening approaches for the older population. For instance, if tumors grow more slowly, with a preclinical detectable period of 6.2 years, as modeled by Boer and colleagues (31), then screening intervals might logically be extended from annual or biannual to every 3 to 5 years. The decrease in the number of mammography films (and evaluations for positive results) and the maintenance of most of the benefits of screening would result in more favorable cost-effectiveness ratios. If some aggressive tumors have a short preclinical phase, then even annual screening will have fewer benefits. It will be important to collect more primary data on age-dependent disease history before suggesting any changes in recommendations about breast cancer screening intervals for older women. For instance, age-stratified data on biomarker profiles, recurrence, and survival for women with similar stage and therapy might be used to draw inferences about key aspects of disease history. Another example of useful data to assess age-related differences in biology is comparisons of the size of tumors in women with clinically detected cancer and women with cancer detected by screening. Since directly observing the course of untreated disease in different age groups is impossible, indirect data can be used to estimate tumor doubling times and mortality in simulation models. Models are also useful to capture the wide range of individual variability in tumor biology that occurs at all ages.

Many women with abnormal test results will not have cancer (false-positive results). Elmore and colleagues (39) estimated that 56% of women screened annually, beginning at age 40 years, will be falsely identified as having cancer and will need to undergo additional films or tests. Although the positive predictive value of mammography increases with age because of increasing incidence and improved test performance, the benefits of continuing to screen must be compared with potential distress related to having a false-positive screening result.

Some potential limitations in the studies we reviewed should be considered in interpreting our results. All but 2 analyses (27, 32) examined cost per life-year gained and did not account for differences in quality of life associated with screening, surveillance, or treatment for cancer. No study specifically examined incremental results for screening women after age 80 years. Almost all studies included a discount rate of 3% to 5% to reflect the fact that future savings are generally valued less than present savings. However, if, as suggested by Kerlikowskies and colleagues (27), older women value future years less than the average (that is, have a higher discount rate, such as 10%), then it will be
Cost-Effectiveness of Screening Mammography beyond Age 65 Years

TERMS, and evaluated regimens limited our ability to definitively conclude the most effective and cost-effective age to stop screening older women. It is difficult to evaluate from the data presented in each report whether differences in the results related mainly to differences in the parameters used or diversity in the model structures. For instance, several reports assumed a fixed mortality reduction with mammography screening on the basis of earlier clinical trials. However, some studies drew divergent conclusions about the effect of screening on observed population mortality trends (40, 41), while other studies modeled assumptions about benefit from data on actual differences in distributions of stage and other parameters before and after the advent of regular screening practices in the population. These observational estimates may be more robust than those based on specific effectiveness assumptions from clinical trial settings, especially since older women were underrepresented in the trials (21).

We also only considered strategies that assumed regular use of mammography. As our understanding of disease biology progresses, more complex strategies, including strategies that triage women at some age (for example, at 65 or 70 years of age), on the basis of specific disease risk markers, genetic mutations, or disease-specific or health status–specific life expectancy, may yield more specific guidance for clinicians and policymakers. The latter guidelines would be most useful if accompanied by tools to rapidly estimate life expectancy on the basis of age and comorbid conditions. New technologies, if more sensitive than mammography and of similar or lower cost, may also be useful in older women. No trial we identified studied the value of clinical breast examination. A long preclinical detectable period for less virulent disease could make this method a cost-effective alternative to radiologic imaging.

Uncertainty about how different model features are applied also potentially limits the ability to draw conclusions from this review. It would help guide screening policy if investigators participated in a validation exercise to compare intermediate and long-term model outcomes by using a common set of variables for a common set of strategies. This would allow assessment of whether conclusions are robust or depended on model structure and assumptions. The consistent finding that screening after age 65 years reduces mortality from breast cancer at reasonable costs supports the general conclusion that screening should continue, especially if a woman is in good health. These findings are consistent with those of large population-based studies showing mortality reduction or downstaging benefits in women older than 75 years of age (42–44), even those with moderate comorbid conditions (45), and with the summary of recommendations for the U.S. Preventive Services Task Force (35). If the preclinical detectable phase of breast cancer is longer in older women than in younger women, a longer screening interval (longer than every 2 years) might be more cost-effective.

This review has important implications for future research and policymaking. It supports the consensus view among major policymaking bodies that breast cancer screening is warranted for older women and that preferences for potential harms and benefits should be considered in screening decisions. Finally, it suggests that further research is needed to understand the parallel natural histories of breast cancer and aging, the impact of knowledge of a breast cancer diagnosis and receipt of treatment on quality of life, time preferences, and rates of adherence to screening and treatment. These data are important to define optimal approaches to avoiding cancer morbidity and maximizing active life expectancy in the older female population, which is growing.

From Georgetown University Medical Center, Lombardi Cancer Center, Washington, DC; Oregon Health and Science University, Portland Veterans Affairs Medical Center, Portland, Oregon; Merck & Co., Inc., West Point, Pennsylvania; University of North Carolina, Research Triangle Institute, Research Triangle Park, North Carolina; Mount Sinai School of Medicine, New York, New York; Agency for Healthcare Research and Quality, Rockville, Maryland; and University of Rochester, Rochester, New York.

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Requests for Single Reprints: Jeanne Mandelblatt, MD, MPH, Lombardi Cancer Center, 2233 Wisconsin Avenue, Suite 317, Washington, DC 20007; e-mail, mandelbj@georgetown.edu.

Current author addresses are available at www.annals.org.
References


Current Author Addresses: Dr. Mandelblatt: Lombardi Cancer Center, 2233 Wisconsin Avenue, Suite 317, Washington, DC 20007.
Dr. Saha: Portland Veterans Affairs Medical Center, 3710 SW U.S. Veterans Hospital Road, Portland, OR 97239.
Dr. Teutsch: Merck & Co., PO Box 4, WP39-168, West Point, PA 19486-0004.
Dr. Hoerger: Research Triangle Institute, 3040 Cornwallis Road, Research Triangle Park, NC 27709.

Dr. Siu: Mount Sinai School of Medicine, 1 Gustave L. Levey Place, Box 1070, New York, NY 10029.
Dr. Atkins: Agency for Healthcare Research and Quality, 540 Gaither Road, 6th Floor, Rockville, MD 20850.
Dr. Klein: University of Rochester, 601 Elmwood, #69, Rochester, NY 14642.
Dr. Helfand: Portland Veterans Affairs Medical Center, 3181 SW Sam Jackson Park Road, Portland, OR 97201.