# Retrospective Cost-effectiveness Analysis of Screening Mammography

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***Background:*** **Many guidelines recommend screening mammography every 1–2 years for women older than 40 years; more than 70% of women now participate in routine screening. No studies have examined the societal impact of screening practices over the past decade in the United States on costs and quality-adjusted life-years (QALYs). We performed a retrospective cost-effectiveness analysis comparing actual and alternative screening mammography scenarios.** ***Methods:*** **We used a discrete-event simulation model of breast cancer epidemiology to estimate the costs and the number of QALYs that were associated with observed screening mammography patterns in the United States from 1990 to 2000 for women aged 40 years or older. We also estimated costs and QALYS for no screening and for 64 alternative screening scenarios. Incremental cost-effectiveness ratios were computed. Sensitivity analyses were performed on key parameters.** ***Results:*** **Actual U.S. screening patterns from 1990 to 2000 accrued 947.5 million QALYs and cost $166 billion over the lifetimes of the screened women, resulting in a gain of 1.7 million QALYs for an additional cost of $62.5 billion compared with no screening. Among those polices that were not dominated—i.e., for which no alternative existed that produced more QALYs for lower costs—screening all women aged 40–80 years annually per some U.S. guidelines was the most expensive option, costing $58 000 per additional QALY gained compared with the next most costly alternative, screening all women aged 45–80 years annually. Many alternative screening scenarios generated more QALYs for less cost (with savings up to $6 billion) than actual screening patterns over the study period. Sensitivity analysis showed that conclusions about the cost-effectiveness of screening mammography policies were highly sensitive to small, short-term detrimental effects on quality of life from the screening test itself.** ***Conclusions:*** **Choosing among the efficient policies to guide current screening recommendations requires consideration of costs to promote participation in screening and measurement of acute quality-of-life effects of mammography. [J Natl Cancer Inst 2006;98:774–82]**

Since its introduction as a screening tool in the 1980s, screening mammography has been widely disseminated in the United States. Mammography guidelines have gradually broadened and now recommend that all women older than 40 years be screened annually or biennially *(1,2)*. In 2001, nearly 70% of U.S. women reported having had a mammogram within the past 2 years *(3)*. Breast cancer mortality rates in the United States have slowly declined over the past decade, probably in part because of the dissemination of screening mammography *(4)*. However, this mortality benefit has been offset by smaller (i.e., nonlethal) but frequent risks associated with mammography, including false-positive test results *(5)*; subsequent, often invasive, diagnostic follow-up tests; and the potential for overdiagnosis *(6)*. With these tradeoffs in mind, an analysis of screening guidelines relative to actual screening performance may help to inform current policies regarding screening mammography.

Previous cost-effectiveness studies *(7–12)* have concluded that, in general, future implementation of screening mammography would be cost-effective compared with no screening. However, none of those studies evaluated the gap in screening performance between recommended guidelines for screening mammography and screening as it has been implemented in the United States historically because none included the observed screening dissemination as a basis for comparison. Furthermore, previous analyses tended to focus on narrow age ranges or on particular age cohorts, not on the entire U.S. population over time. Because the choice of study population can potentially affect the cost-effectiveness of medical interventions *(13)* and because breast cancer risk and the accuracy of screening mammography are functions of age, it is important to evaluate screening mammography practices across the entire population that would be affected.

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*See* "Notes" following "References."

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Recently, positive new light has been shed on the debate over the effectiveness of screening mammography for reducing breast cancer mortality. A consortium of investigators who used seven independent statistical and simulation models of the natural history of breast cancer reported that routine screening use has contributed to the observed reduction in U.S. breast cancer mortality seen over the last 25 years *(14,15)*. Given this new evidence, we have used one of those seven models to conduct a cost-effectiveness analysis of screening mammography. Our analysis posed a different question from that posed by many cost-effectiveness analyses. Specifically, we retrospectively examined the cost-effectiveness of screening programs for the U.S. female population for 1990–2000. We asked what happens to the total expenditures and quality-adjusted life-years (QALYs) if other screening practices, many of them congruent with recommended guidelines, had been substituted for the actual screening practices of the 1990s. We considered observed screening patterns as well as no screening and alternative screening scenarios that encompass U.S. guidelines to evaluate how effectively resources are actually being spent to improve women's health in the United States.

## Methods

### Model Overview

To compute total costs and health effects associated with different screening mammography scenarios, we used a discrete-event simulation model of breast cancer epidemiology in a population over time that was developed at the University of Wisconsin as part of the National Cancer Institute's Cancer Intervention and Surveillance Modeling Network. One of the original purposes of this model was to investigate the individual and combined contributions of changes in mammography screening and adjuvant therapies for breast cancer from 1975 through 2000 to the observed reductions in breast cancer mortality from 1990 through 2000 *(14)*. As such, the model incorporates secular trends in breast cancer risk, screening use, and treatment dissemination. By simulating the individual life histories of women aged 20 years or older who were born in 1891 through 1980 in proportion to their prevalence in the U.S. population and aggregating the outcomes, the model can replicate population-level U.S. cancer surveillance data corresponding to calendar years 1975 through 2000.

An overview of model structure relevant to this analysis is provided here. Unobservable model parameters that controlled the natural history and detection of breast cancer were estimated through the process of calibration to fit observed age-adjusted, stage-specific breast cancer incidence data from the Surveillance, Epidemiology, and End Results (SEER) program *(16)* and breast cancer mortality data for 1975 through 2000 reported by National Center for Health Statistics (National Center for Health Statistics, National Health Interview Survey Web site http://www.cdc.gov/nchs/deaths.htm links to survey description documentation and data). The model has been cross-validated against data from the Wisconsin Cancer Reporting System, a cancer registry independent of SEER *(17)*. Separate analyses based on this model produced results that were congruent with those from analyses based on other models of the natural history of breast cancer *(17)*. Model design, assumptions, and validation have also been described elsewhere *(17–19)* and are available at http://www.cisnet.cancer.gov/profiles.

### Model Specification

Individual life histories were generated through four model components: the natural history of breast cancer, breast cancer detection, breast cancer treatment, and breast cancer mortality. The natural history component modeled breast cancer occult inception and progression as a function of a woman's birth year and current age. Secular trends in breast cancer incidence that account for changes in risk factor prevalence were incorporated into the likelihood of cancer onset *(20)*. After onset, breast cancers were assumed to progress in disease stage according to a stochastic Gompertz-type growth model that controls the size and the extent of the tumors *(21–24)*. Tumors were assigned a SEER historical stage (in situ, localized, regional, or distant) based on tumor size and spread to lymph nodes at time of diagnosis in the model for statistical tabulation. It is assumed that not all in situ or small localized invasive cancers progress to be a lethal threat to the woman *(17)*.

Breast cancer can be detected by either of two methods: screening mammography or routine clinical detection (i.e., self and/or clinical breast examinations). In the model, the sensitivity of mammography and the likelihood of a routine clinical detection were functions of a woman's age and tumor size. Also, the sensitivity of mammography was assumed to improve over time, corresponding to improvements in mammographic technology. These parameters were estimated via model calibration and correspond to estimates of sensitivity derived from observational data, which ranged from 60% to 90% *(25–27)*. Specificity of mammography, a function of age, ranges from 88% to 90% *(28)*. Routine clinical detection was also assumed to improve over time, coinciding with increasing dissemination of mammography and of the awareness by both women and physicians of breast cancer as a disease. In the model, routine clinical detection could occur at any time, whereas the timing of screening mammograms was based on the assigned screening scenario. Screening scenarios considered in this analysis are described in a following section.

The model assumed that all women received treatment at the time of breast cancer detection. Adjuvant therapy with chemotherapy and/or tamoxifen was assigned in accordance with observed U.S. dissemination patterns *(29)*. The effectiveness of treatment was a function of age at diagnosis, tumor characteristics (stage at detection and estrogen receptor status), and receipt of adjuvant treatment *(30,31)*, and was modeled independent of the method of breast cancer detection. An effective treatment was assumed to halt breast cancer progression.

In the model, death could be due to breast cancer or to other causes. We used U.S. birth cohort–based life tables, with breast cancer as a cause of death removed *(32,33)*, to assign date of death due to causes other than breast cancer to each woman. A date of death from breast cancer based on mortality derived from women who were diagnosed with distant-stage disease in the SEER program *(16)* was assigned to a woman after her breast cancer progressed to the distant or metastatic stage. The timing and cause of death were determined by the earlier of the two dates of death (breast cancer or other causes).

### Quality of Life

Age-specific quality-of-life utility weights were specified for four health states: healthy; breast cancer diagnosed and treated in the in situ or localized stage; breast cancer diagnosed and treated in the regional stage; and distant-stage breast cancer (Table 1).

**Table 1.** Yearly quality-of-life weights

| Age (y) | Health state | | | | | |
|---|---|---|---|---|---|---|
| | Healthy* | In situ or localized breast cancer† | Regional breast cancer‡ | Distant breast cancer§ | Mammogram with negative result‖ | Mammogram with positive result¶ |
| 30–34 | 0.856 | 0.770 | 0.642 | 0.513 | 0.852 | 0.841 |
| 35–39 | 0.833 | 0.750 | 0.625 | 0.500 | 0.829 | 0.819 |
| 40–44 | 0.829 | 0.746 | 0.622 | 0.497 | 0.825 | 0.815 |
| 45–49 | 0.804 | 0.724 | 0.603 | 0.482 | 0.800 | 0.790 |
| 50–54 | 0.780 | 0.702 | 0.585 | 0.468 | 0.776 | 0.767 |
| 55–59 | 0.747 | 0.672 | 0.560 | 0.448 | 0.744 | 0.734 |
| 60–64 | 0.745 | 0.670 | 0.558 | 0.447 | 0.741 | 0.732 |
| 65–69 | 0.734 | 0.660 | 0.550 | 0.440 | 0.730 | 0.721 |
| 70–75 | 0.716 | 0.645 | 0.537 | 0.430 | 0.713 | 0.704 |
| 75–79 | 0.675 | 0.608 | 0.507 | 0.405 | 0.672 | 0.664 |
| 80–84 | 0.623 | 0.561 | 0.467 | 0.374 | 0.620 | 0.612 |
| ≥85 | 0.590 | 0.531 | 0.442 | 0.354 | 0.587 | 0.580 |

*The quality-of-life weights for the healthy state were the mean EQ-5D scores for each age group computed from year 2000 Medical Expenditure Panel Survey data. A woman was in this health state and was assigned these weights if she did not have diagnosed breast cancer. Her quality-of-life weight was assigned based on her current age.

†Quality-of-life weights for the in situ or localized breast cancer health state were assumed to be 90% of the values for a healthy woman. A woman entered this health state if breast cancer was diagnosed in the in situ or localized state and remained in this state for 2 years after which time a woman returned to the healthy state. During that 2 year period, she was assigned these quality-of-life weights based on her current age.

‡Quality-of-life weights for the regional breast cancer state were assumed to be 75% of the healthy state. A woman entered this health state if breast cancer was diagnosed in the regional state and remained in this state for 2 years after which time a woman returned to the healthy state. During that 2 year period, she was assigned these quality-of-life weights based on her current age.

§Quality-of-life weights for the distant breast cancer state were assumed to be 60% of the healthy state. A woman entered this health state if either breast cancer was diagnosed in the distant state or her breast cancer progressed to the distant state as dictated by the underlying tumor growth model. A woman remained in this state until her death and was assigned these quality-of-life weights based on her current age.

‖This health state was used for the sensitivity analysis only. In the sensitivity analysis, a woman entered this health state during the time cycle of a negative screening mammogram. The quality-of-life weight corresponds to 7 days at 25% of the healthy state and the remaining time in healthy. It captures potential short-term decrements in quality of life (e.g., anxiety) that may occur as the result of a screening mammogram itself. On the basis of her current age, a woman was assigned these quality-of-life weights for the time cycle in which she had a negative screening mammogram.

¶This health state was used for the sensitivity analysis only. In the sensitivity analysis, a woman entered this health state during the time cycle of a false positive screening mammogram. The quality-of-life weight corresponds to 25 days at 25% of the healthy state and the remaining time in healthy. It captures potential short-term decrements in quality of life (e.g., anxiety) that may occur as the result of a false-positive screening mammogram. On the basis of her current age, a woman was assigned these quality-of-life weights for the time cycle in which she had a positive screening mammogram.

The age-specific quality-of-life utility weights for healthy women were derived from EuroQol EQ-5D quality-of-life utility scores. The EQ-5D is a widely used utility-based measure for general health *(34)*. These data were collected in the 2000 wave of the Medical Expenditure Panel Survey, a nationally representative survey of health care usage, insurance, and costs in the United States (http://www.meps.ahrq.gov/). We used percentages of the age-specific EQ-5D scores for healthy women to estimate the potential negative effects of a breast cancer diagnosis and treatment on a woman's quality of life for a limited period. Our values were consistent with treatment-specific quality-of-life weights reported in other studies *(35)*. We assigned a utility weight for every 6-month period in a woman's lifetime; the sum of those weights across the woman's lifetime equaled the QALYs accrued for that woman *(13)*.

## Costs

The costs incorporated into the model (Table 2) included the average cost of a screening mammogram ($70), the average cost of diagnostic follow-up to a positive or abnormal screening result or the average cost of diagnosis from clinical detection ($533), and the treatment costs (range: $12 000–$27 000 depending on the stage at detection of breast cancer; treatment costs include the costs of initial treatment, of continuing treatment, and of terminal treatment for in situ, localized, regional, distant) *(36–38)*. Indirect costs associated with time and travel to and from the test and future medical care costs were not included in this analysis. All cost estimates were adjusted to calendar year 2000 dollars by using the medical care component of the Bureau of Labor Statistics Consumer Price Index *(39)*.

## Screening Scenarios

Actual screening patterns were replicated by stochastically assigning women to an age at first screening mammogram and to a subsequent screening frequency that was in accordance with observed U.S. dissemination and usage patterns *(40)*. These mammography dissemination and usage patterns, which were composed of a mixture of frequent and infrequent screening patterns and included non-users, were informed by and are consistent with data from the National Health Interview Survey (National Center for Health Statistics, National Health Interview Survey Web site http://www.cdc.gov/nchs/nhis.htm) and the Breast Cancer Surveillance Consortium (http://breastscreening.cancer.gov/) *(41)*. Under this screening scenario in the simulation model, the percentage of women who had never been screened by mammography decreased from 75% in 1985 to 25% in 2000 and the percentage of women who were screened every 1 or 2 years increased from 20% to 50% *(15,40)* and population participation in screening mammography increased from 0% in the early 1980s to nearly 70% in 2000, closely replicating

**Table 2.** Costs associated with breast cancer screening and treatment

| Procedure (ref) | Cost (in year 2000 USD) |
|---|---|
| Screening mammogram *(37)* | 70 |
| Diagnostic workup* *(37)* | 533 |
| Treatment costs by stage at diagnosis *(38)* | |
| Initial treatment for the first 6 mo after diagnosis | |
| In situ | 11 682 |
| Localized | 14 865 |
| Regional | 16 837 |
| Distant | 0 |
| Continuing treatment for the subsequent 3 mo after initial treatment | |
| In situ | 1218 |
| Localized | 1314 |
| Regional | 1952 |
| Distant | 4007 |
| Terminal treatment for the last 6 mo of life | |
| In Situ | 15 396 |
| Localized | 20 527 |
| Regional | 27 881 |
| Distant | 25 559 |

*Diagnostic workup was assumed to include a diagnostic mammogram and a biopsy.

age-specific screening participation patterns observed in the United States during this period *(3)*.

The "no screening" scenario assumed no mammographic screening in the population after 1989. Sixty-four additional scenarios, each with a particular fixed screening schedule beginning in 1990, were modeled. The fixed-schedule scenarios varied by the age at the first screen (40, 45, 50, or 55 years) and at the last screen (65, 70, 75, or 80 years) and by the screening interval (1, 2, 3, or 5 years). To mimic the initiation of a new screening program, we assumed that all women in the age range indicated by the screening scenario participated and that in 1990, the starting year, all women in the age range specified by the screening scenario began screening. Because past screening use affects current screening outcomes *(18)* and thus may affect the cost-effectiveness of the screening programs for all scenarios, including the no-screening scenario, we assumed that the actual (historical) screening dissemination patterns had occurred before the start of the study in 1990. This assumption makes the "actual practice" scenario consistent with the full history of screening practices, so that each of the other scenarios represents a hypothetical change to historical practices beginning in 1990.

### Cost-effectiveness Analysis

Our analysis examined the performance of screening mammography from 1990 to 2000. The population investigated included all women in the United States who were aged 40 years or older during the study period, comprising birth cohorts from 1891 to 1960 and representing approximately 95 million women. The women received screening mammograms during this 10-year period in accordance with the specified screening scenario. The costs and effects of screening, of a breast cancer diagnosis, and of treatment for breast cancer were calculated for each woman starting in calendar year 1990 and ending on the date of her death. For women who died after calendar year 2000, rates of breast cancer onset, detection by routine clinical finding, and treatment effectiveness were defined according to the prevailing rates in the year 2000. Evaluations of the costs and effects of the screening scenarios were meant to capture the lifetime effects of the 10-year period of screening in the population. A 3% annual discount rate was applied to both costs and QALYs, as recommended by the Panel on Cost-effectiveness in Health and Medicine *(13)*.

We conducted a separate run of the simulation model for each screening scenario to compute the total costs and QALYs for that scenario; each run of the model used the same period; natural history assumptions, including those underlying the onset of breast cancer; and population. A unique feature of the model is that it uses common random numbers, a technique of variance reduction *(42,43)* in which the same random number sequences are used across runs. This technique allows for counterfactual analyses because the same population of women is compared across screening scenarios. Thus the population under investigation at the start of the analysis in 1990 was identical in the prevalence of underlying breast cancer across all screening scenarios. Therefore, differences in costs and QALYs across scenarios are the direct result of the screening pattern assigned to each woman and their consequent effects on health. For each screening scenario, this process was repeated 25 times by using different random numbers to generate a distribution of results. Outputs are reported as the mean and 95% confidence interval (CI) for the replications. These confidence intervals provide an indication of variation due to stochastic sources of variation within the model.

### Sensitivity Analyses

In general, the purpose of a cost-effectiveness analysis is to construct a model that produces as meaningful an estimate as possible of the costs, QALYs, and incremental cost-effectiveness ratios of different interventions *(13)*. Traditional statistical hypothesis testing is not appropriate. Instead, to understand the effect of key model parameters and assumptions on the stability of the incremental cost-effectiveness ratios, sensitivity analyses are performed *(13)*. In a sensitivity analysis, cost-effectiveness ratios are recomputed by changing influential model variables. The extent of change in the ratios provides an indication of the robustness of model conclusions due to model uncertainty. For our sensitivity analysis, we varied the level of population participation in the alternative screening scenarios and the quality of life associated with a screening mammogram across plausible ranges. Costs, QALYs, and incremental cost-effectiveness ratios were recomputed with these changes in parameter values and compared with our initial result to isolate the effect of that parameter on the conclusions drawn about the cost-effectiveness of screening mammography.

## Results

### Actual Screening Patterns

The actual screening patterns for women aged 40 years or older resulted in 947.5 million QALYs (1.596 billion QALYs undiscounted) at a total cost of $166 billion ($301 billion undiscounted) for breast cancer detection and treatment. These totals reflect the observed history of screening dissemination in the United States from 1990 to 2000 and the future effects of this decade of screening on the population. By comparison, in the absence of any screening during the 1990s (no-screening scenario), 945.8 million QALYs (1.592 billion QALYs undiscounted) would have accrued at a cost of $103 billion ($199 billion undiscounted) as a result of routine clinical detection and subsequent

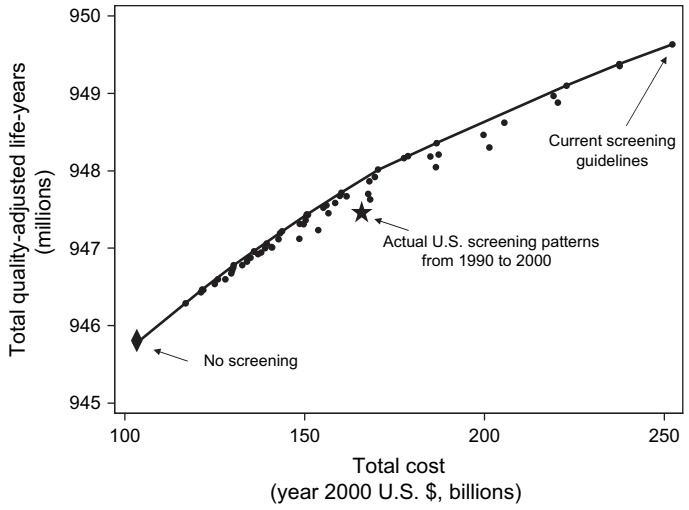


**Fig. 1.** Costs and quality-adjusted life-years associated with simulated screening policies. Each dot represents one of the 64 alternative policies analyzed. The **solid line** connects the efficient policies (i.e., policies for which no alternative policy exists that results in more quality-adjusted life-years for lower costs). The **star** indicates the cost and quality-adjusted life-years associated with actual U.S. screening patterns, which consisted of a mixture of frequent and infrequent screening patterns and included non-users. The **diamond** shows the cost and quality-adjusted life-years associated with no screening after 1990. Total quality-adjusted life-years and total cost were discounted at 3%.

treatment. Therefore, as a result of the screening program in place during the 1990s, U.S. women gained 1.7 million QALYs at an additional cost of nearly $63 billion. The model also predicts that, with screening, approximately 25% more breast cancers were detected overall compared with no screening.

### Alternative Screening Scenarios

The total costs of the alternative scenarios ranged from $117 billion to $252 billion ($219 billion to $426 billion undiscounted, respectively), and the total QALYs accrued ranged from 945.3 million to 949.6 million (1.593 billion to 1.602 billion QALYs undiscounted, respectively). The screening scenarios with the shorter screening intervals and the broader age ranges were the most costly but accrued the most QALYs. Figure 1 depicts the total costs and QALYs accrued for all simulated scenarios and for actual screening patterns and no screening. The no-screening scenario was the least costly option and accrued the fewest QALYs. Scenarios that had higher costs and that accrued fewer QALYs were dominated by scenarios that accrued more QALYs for the same or lower cost. In Fig. 1, the solid line that connects the 11 screening scenarios that were not dominated (i.e., the "efficient" policies in economic terminology, that is, policies for which no alternative policy exists that results in more QALYs for lower costs), represents the efficient frontier (i.e., the set of efficient policies) *(13)*.

Actual screening practice from 1990 to 2000, depicted by the star in Fig. 1, was not on the efficient frontier; many of the alternative scenarios achieved more QALYs for the same or lower costs. For example, compared with the actual screening patterns over the study period, implementing the efficient strategy of screening all women aged 45–70 years every 3 years could have saved approximately $6 billion while accruing an equivalent number of QALYs.

### Cost-effectiveness Analysis

To understand the relative performance of the efficient screening scenarios, we performed an incremental cost-effectiveness analysis. Incremental cost-effectiveness ratios were computed by comparing the differences in costs and QALYs between the efficient policies ranked in increasing order of costs. Table 3 shows total costs, total QALYs, and incremental cost-effectiveness ratios for the 11 efficient scenarios.

Screening and treatment for the scenario of screening all women aged 55–70 years every 5 years would cost $27 000 per additional QALY compared with no screening. Screening the same age group but increasing the frequency of screening to every 3 years would cost $28 000 per additional QALY. The incremental increase in QALYs became increasingly expensive as the age ranges became wider and the screening frequency increased.

Policies that resemble current U.S. guidelines for mammography screening (e.g., screening all women aged 40–80 years annually) were on the efficient frontier. However, they were also the most costly screening scenarios as shown by their location in the upper right tail of the frontier in Fig. 1. Screening all women in the United States aged 40–80 years every year resulted in a

**Table 3.** Costs, QALYs, and incremental cost-effectiveness ratios for efficient screening scenarios*

| Age at first screen, y | Age at last screen, y | Screening interval, y | Mean cost†, billion $ (95% CI) | Mean No. of QALYs†, millions (95% CI) | Incremental cost per QALY‡, $ (95% CI) |
|---|---|---|---|---|---|
| No screening | | | 103 (102.5 to 103.7) | 945.8 (945.3 to 946.3) | — |
| 55 | 70 | 5 | 121 (120.9 to 122.1) | 946.5 (946.0 to 947.0) | 27 000 (25 000 to 28 000) |
| 55 | 70 | 3 | 130 (129.6 to 130.8) | 946.8 (946.3 to 947.3) | 28 000 (24 000 to 32 000) |
| 50 | 75 | 3 | 144 (143.1 to 144.3) | 947.2 (946.7 to 947.7) | 31 000 (26 000 to 37 000) |
| 45 | 75 | 3 | 151 (150.0 to 151.1) | 947.4 (946.9 to 947.9) | 31 000 (24 000 to 40 000) |
| 50 | 75 | 2 | 160 (159.6 to 160.8) | 947.7 (947.2 to 948.2) | 34 000 (27 000 to 42 000) |
| 45 | 75 | 2 | 170 (169.8 to 171.0) | 948.0 (947.5 to 948.5) | 34 000 (27 000 to 42 000) |
| 40 | 80 | 2 | 187 (186.1 to 187.2) | 948.4 (947.8 to 948.9) | 47 000 (41000 to 54 000) |
| 45 | 75 | 1 | 223 (222.2 to 223.3) | 949.1 (948.6 to 949.6) | 49 000 (44 000 to 54 000) |
| 45 | 80 | 1 | 237 (236.9 to 238.0) | 949.4 (948.9 to 949.9) | 53 000 (49 000 to 56 000) |
| 40 | 80 | 1 | 252 (251.6 to 252.8) | 949.6 (949.1 to 950.2) | 58 000 (47 000 to 71 000) |

*QALYs = quality-adjusted life-years; CI = confidence interval.

†Reported as the mean value (95% CI) for 25 replications of the simulation model. Discounted at 3% per year.

‡The difference in costs divided by the difference in QALYs for each strategy compared with the next most expensive strategy. Linear 95% confidence intervals for the ratios are reported.

gain of more than 2 million QALYs at an incremental cost of $87 billion more than the cost of actual screening patterns (i.e., 949.6 million at a cost of $252 billion for the policy resembling the guidelines, compared with 947.5 million QALYs at a cost of $166 billion for actual screening patterns), a cost of $40 000 per additional QALY. Most of these additional costs are from the screening mammograms themselves and their associated follow-up, because the model predicted that more than 2.4 times more mammograms would be performed under this scenario than under actual screening practice. As a result of these additional mammograms, many more women would experience a false-positive mammogram, but there would be 25% fewer breast cancer deaths over the lifetimes of this population compared with the number of breast cancer deaths observed under actual screening patterns. (Supplementary Table 1, containing additional simulation model outcomes, including the number of mammograms, the number of screen and clinical detected cases, and the number of breast cancer deaths for each screening scenario, can be found at http://jncicancerspectrum.oxfordjournals.org/jnci/content/vol98/issue11.)

### Sensitivity Analysis

We found that the results were sensitive to the level of population participation in the alternative screening scenarios. Our initial assumption for these scenarios was 100% participation from the onset of the screening program in 1990 to the end of the study in 2000. Actual participation rates were considerably less than 100% over the study period, ranging from approximately 40% in 1990 to approximately 70% in 2000 *(3)*. Figure 2 compares the screening scenarios under three population participation rates: 100% (initial assumption), 70%, and 50%. With 50% participation, both the costs and the QALYs achieved in the screening scenarios were reduced compared with those for higher participation; the efficient frontier shifted downward and approached the total cost and QALYs achieved by actual screening patterns. Thus, actual screening patterns appear efficient compared with the efficient screening scenarios under the assumption of 50% participation but not under the assumption of 100% participation.

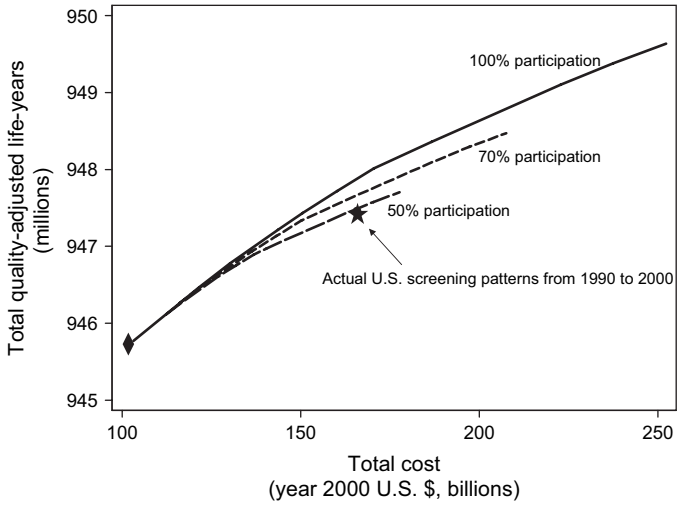


**Fig. 2.** Sensitivity analysis comparing 100%, 70%, and 50% participation in the simulated screening policies. Costs and quality-adjusted life-years are shown for the efficient policies for each of the participation assumptions. The upper efficient frontier (**solid line**) shows the performance assuming 100% population participation and is the same as in Fig. 1. The two lower lines show the efficient frontiers under assumptions of 70% (**short-dashed line**) and 50% (**long-dashed line**) participation from the onset of the screening program in 1990. The **star** indicates the cost and quality-adjusted life-years associated with actual U.S. screening patterns, which consisted of a mixture of frequent and infrequent screening patterns and included nonusers, and remained unchanged under various assumptions about population participation in the alternative screening scenarios. The **diamond** shows the cost and quality-adjusted life-years associated with no screening after 1990.

Model conclusions about the efficiency of screening scenarios were also sensitive to assumptions about quality-of-life effects associated with screening mammography itself. In the first analysis, we assumed that the screening mammogram per se did not affect quality of life. In sensitivity analyses, we assumed that screening participation had small, short-term detrimental effects on quality of life, an approach used in other analyses *(44)*. We also assumed that false-positive mammograms had a somewhat larger detrimental effect on quality of life than routine mammograms. The quality-of-life weights associated with these assumptions are listed in Table 1. As expected, inclusion of these small, short-term decrements to quality of life following a screening mammogram reduced the QALYs gained from the screening scenarios, an effect that was more pronounced in the scenarios with more frequent screening. Thus, because the costs were not affected by the quality-of-life assumption but the QALYs were reduced, the efficiencies of screening scenarios that recommend more frequent screening for more women were also reduced. For example, whereas the cost per additional QALY for screening all women aged 40–80 years every year compared with current practice was $40 000 in the analysis that assumed no quality-of-life effects, this ratio increased to $128 000 per additional QALY when detrimental quality-of-life effects for a screening mammogram were included.

Table 4 shows results of the incremental cost-effectiveness analysis of the efficient screening scenarios that included the assumption about the detrimental quality-of-life effects associated with a screening mammogram. The set of efficient policies under this assumption differed slightly from those under the original analysis. Screening women aged 40–80 years every year in accordance with current U.S. guidelines was no longer among the efficient policies. The broadest and most intense screening scenario among the efficient policies was one that screened women aged 45–80 years every year at a cost of more than $300 000 per additional QALY accrued beyond those accrued by screening women aged 45–80 years every 2 years.

## Discussion

We estimated that, compared with no screening, the gain in total QALYs from actual screening practice was 1.7 million QALYs for the study population of 95 million women. This gain of 0.02 QALYs per woman (or 0.05 QALYs per woman, undiscounted) in the population from 10 years of the current screening practices may appear to be small. However, many more women participate in screening mammography than actually benefit, as indicated by the low incidence of breast cancer. Our estimate of a gain of 0.02 QALYs per woman is consistent in magnitude with the health gains reported from breast cancer screening programs specifically and in general for screening and prevention programs for other diseases *(11,45)*.

Compared with no screening during the study period (1990–2000), the prevailing screening mammography practices incurred

**Table 4.** Sensitivity analysis for inclusion of quality-of-life effects from a screening mammogram: costs, QALYs, and incremental cost-effectiveness ratios for efficient screening scenarios*

| Age at first screen, y | Age at last screen, y | Screening interval, y | Mean cost†, billion $ (95% CI) | Mean No. of QALYs†, millions (95% CI) | Incremental cost per QALY‡, $ (95% CI) |
|---|---|---|---|---|---|
| No screening | | | 103 (102.5 to 103.7) | 945.8 (945.3 to 946.3) | — |
| 55 | 70 | 5 | 121 (120.9 to 122.1) | 946.2 (945.7 to 946.7) | 43 000 (39 000 to 47 000) |
| 55 | 70 | 3 | 130 (129.6 to 130.8) | 946.4 (945.9 to 946.9) | 46 000 (34 000 to 58 000) |
| 55 | 75 | 3 | 136 (135.3 to 136.5) | 946.5 (946.0 to 947.0) | 51 000 (45 000 to 57000) |
| 55 | 75 | 2 | 150 (149.9 to 151.1) | 946.7 (946.2 to 947.3) | 60 000 (43 000 to 77 000) |
| 50 | 75 | 2 | 160 (159.6 to 160.8) | 946.9 (946.4 to 947.4) | 79 000 (34 000 to 124 000) |
| 45 | 75 | 2 | 170 (169.8 to 171.0) | 947.0 (946.5 to 947.5) | 84 000 (30 000 to 138 000) |
| 45 | 80 | 2 | 179 (178.0 to 179.3) | 947.1 (946.6 to 947.6) | 100 000 (86 000 to 114 000) |
| 45 | 80 | 1 | 237 (236.9 to 238.0) | 947.2 (946.7 to 947.8) | 341 000 (213 000 to 469 000) |

*QALYs = quality-adjusted life-years; CI = confidence interval.

†Reported as the mean value (95% CI) for 25 replications of the simulation model. Discounted at 3% per year.

‡The difference in costs divided by the difference in QALYs for each strategy compared with the next most expensive strategy. Linear 95% confidence intervals for the ratios are reported.

an additional $63 billion in screening, diagnosis, and treatment expenses over the lifetimes of the women in the population to achieve the 0.02 QALY per woman gain. Although $63 billion is a large expenditure in total, it is an attractive investment if one considers the commonly accepted benchmark for cost-effectiveness of $50 000 per QALY *(46)*; we found that the incremental cost per QALY accrued was approximately $37 000 for actual screening patterns compared with no screening. It is difficult to directly compare this result with those of previously published analyses because past results varied considerably, in part because of differences in the analytic assumptions (including the age structure of the study population, incorporation of past screening, and quality adjustment of life-years and screening scenarios evaluated) *(7,47)*. However, our results reiterate the overall conclusion from these previous analyses that, in general, a screening mammography program can be cost-effective compared with no screening *(8,11,46,48)*.

When we compared actual screening patterns with alternative screening scenarios, the results suggested that there is room for improvement in current screening mammography practice. In Fig. 1, screening scenarios located on the efficient frontier above and to the left of the actual practice scenario (starred) gained the same or more QALYs at the same or lower costs. However, these scenarios were generally less inclusive or intensive than the current screening recommendations and thus are unlikely to be acceptable to the general public. Screening scenarios located on the efficient frontier above and to the right of the actual practice scenario are polices that gained more QALYs compared with current practice, although they did so at a higher cost. Although substantial gains in QALYs relative to observed practice could have been achieved by these policies, all of which would be judged to be attractive investments (less than $50 000/QALY) if compared incrementally with observed practice, the total expenditures associated with these policies are large and this fact should be factored into decisions about future improvements to current screening mammography practice. There are caveats to this conclusion, however, and we turn to them next.

Two additional aspects of the screening program appear to be important for assessing its costs and effectiveness beyond those accounted for in a cost-effectiveness ratio: the costs required to increase participation, and the potentially detrimental quality-of-life effects associated with a screening mammogram. Compared with the actual screening rate in 2000, annual screening with a participation rate of 100% among women aged 40–80 years, as called for by some current U.S. recommendations (i.e., the most expensive policy in Table 3), would incur increased costs and also gain QALYs. The increased costs would result from additional mammograms, additional follow-up testing, and treatment. The gain in QALYs would result from additional reduced breast cancer mortality. Compared with current practice, the additional QALYs would cost $40 000 per QALY. However, this figure does not include the costs of attaining 100% screening participation. Although costs to increase participation have rarely been examined in previous cost-effectiveness analyses for screening mammography, Mandelblatt et al. *(49)* provided an example in which screening programs may not always remain cost-effective when these costs are included. Our population analysis suggested that we could spend as much as $20 billion (or $34 per woman per year for the population of 95 million women for the 10-year screening period) to increase participation and still keep the incremental cost-effectiveness ratio lower than the commonly accepted threshold of $50 000 per QALY (i.e., adding up to $20 billion for increasing participation to the total costs of current screening practice would raise the cost per QALY from $37 000 to approximately $50 000). However, even though such an expenditure would be cost-effective, it is large enough in total magnitude that total costs as well as cost-effectiveness may be an important consideration in policy-making decisions concerning an expenditure of this amount. Paying to promote adherence to less-intensive screening protocols (i.e., policies less far out on the efficient frontier curve in Fig. 1 but still to the right of the star) would incur less total costs and still gain many incremental QALYs.

The second factor to consider with respect to evaluating screening policies is the short-term pain and anxiety reported by some women after a screening mammogram—in particular, after a false-positive screening mammogram *(50–53)*. Modeling these transient health states is difficult. Nonetheless, based on our results it appears to be important to account for small yet common negative effects associated with mammography in the design and evaluation of a screening program, especially because of the high risk of a false-positive test result *(5,54)*. We found that incorporating modest negative quality-of-life effects due to the screening mammogram itself attenuated the QALYs achievable from screening, thus dramatically increasing the incremental cost per

QALY for alternative screening scenarios. For example, the cost per additional QALY accrued to achieve 100% participation for all women aged 40–80 years in annual screening from actual practice was $128 000 when a modest disutility was included. Any additional spending to increase participation in recommended screening programs would increase the cost per QALY even further beyond the $50 000/QALY threshold. Because women's perceptions of potential negative quality-of-life effects from the mammogram itself may contribute to lower participation rates, perhaps a substantial portion of the $34 per woman per year that would be required to increase participation could be spent to reduce women's apprehensions concerning physical discomfort from a mammogram; this approach would promote the double effect of increasing QALYs and participation. In any event, policies that appear societally attractive from the perspective of incremental costs and benefits appear considerably more complicated when the disutility of the mammogram itself is considered.

Our analysis has limitations. First, the natural history of breast cancer was unobservable. As with any model, unobservable parameters were constrained by structural assumptions and relevant parameters that were fit from the data. In developing our simulation model, we fit our submodel of the natural history and progression of breast cancer by using 25 years of SEER data. Our assumptions about the natural history of breast cancer were biologically plausible, and the model produced results that were consistent with observed U.S. trends in breast cancer incidence and mortality *(17)* and with other models of the natural history of breast cancer *(15)*. Second, our analysis focused on the direct medical costs associated with breast cancer screening, follow-up, and treatment. A full societal approach would incorporate personal time costs for women being screened, followed up, and treated—data that we did not have. Incorporating these personal time costs would further reduce the amount of money that could be spent on increasing participation. Finally, we did not consider screening strategies that specified screening age ranges and frequency by individual risk of breast cancer. A future direction is to explore these types of stratified screening strategies that differentially target women who may be at higher risk for breast cancer with more frequent screening.

Current breast cancer screening practice appears to have contributed substantially to the health of women in the United States. However, because many of the alternative screening scenarios examined in our analysis were more effective and less costly than the actual screening patterns from 1990 to 2000, it is likely that current screening programs can be improved. Choosing among the efficient policies to guide current screening recommendations is a complex, high-level decision that is beyond the scope of one cost-effectiveness analysis. Policies directed to moving from current screening practice to full participation in current guidelines (i.e., annual screening for all women aged 40 years or older) are attractive from a cost-effectiveness standpoint. Yet, they are expensive investments in total magnitude. Our analysis identifies other important factors that should also be considered in guiding future screening policy, including the costs of increasing participation and of short-term disutility associated with a mammogram. An investment in studies that will provide empiric data on these two important quantities should be a high priority for policy makers who are hoping to improve population-based programs for breast cancer screening.

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## Notes

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