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Incorporating Baseline Breast Density When Screening Women at Average Risk for Breast Cancer:

A Cost-Effectiveness Analysis

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Abstract

Background: Breast density classification is largely determined by mammography, making the timing of the first screening mammogram clinically important.

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Objective: To evaluate the cost-effectiveness of breast cancer screening strategies that are stratified by breast density.

Design: Microsimulation model to generate the natural history of breast cancer for women with and those without dense breasts and assessment of the cost-effectiveness of strategies tailored to breast density and nontailored strategies.

Data Sources: Model parameters from the literature; statistical modeling; and analysis of Surveillance, Epidemiology, and End Results–Medicare data.

Target Population: Women aged 40 years or older.

Time Horizon: Lifetime.

Perspective: Societal.

Intervention: No screening; biennial or triennial mammography from age 50 to 75 years; annual mammography from age 50 to 75 years for women with dense breasts at age 50 years and biennial or triennial mammography from age 50 to 75 years for those without dense breasts at age 50 years; and annual mammography at age 40 to 75 years for women with dense breasts at age 40 years and biennial or triennial mammography at age 50 to 75 years for those without dense breasts at age 40 years.

Outcome Measures: Lifetime costs and quality-adjusted life-years (QALYs), discounted at 3% annually.

Results of Base-Case Analysis: Baseline screening at age 40 years followed by annual screening at age 40 to 75 years for women with dense breasts and biennial screening at age 50 to 75 years for women without dense breasts was effective and cost-effective, yielding an incremental cost-effectiveness ratio of \$36 200 per QALY versus the biennial strategy at age 50 to 75 years.

Results of Sensitivity Analysis: At a societal willingness-to-pay threshold of \$100 000 per QALY, the probability that the density-stratified strategy at age 40 years was optimal was 56% compared with 6 other strategies.

Limitation: Findings may not be generalizable outside the United States.

Conclusion: The study findings advocate for breast density–stratified screening with baseline mammography at age 40 years.

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Breast cancer is the most frequently diagnosed cancer and the second leading cause of cancer deaths for women in the United States, accounting for over 279 100 new cases and 42 690 cancer deaths in 2020 (1). Although attention to breast density has been growing among patient advocacy groups, legislators, and the media in the past decade, the association between dense breasts and high risk for breast cancer was established as early as 1976 (2). The Breast Imaging Reporting and Data System (BI-RADS) classification system groups breast density into 4 categories on mammographic reports: almost entirely fatty (A), scattered areas of fibro-glandular density (B), heterogeneously dense (C), and extremely dense (D). Dense breasts include BI-RADS category C and D, and the estimated prevalence among women in the United States is around 50% (3).

Compared with other risk factors for breast cancer that can be detected from genetic testing (for example, *BRCA1/2* mutation) or through information intake at clinical encounters (such as family history of cancer or prior radiation therapy to the chest), a woman's breast density is largely determined through mammography. This presents a challenge for determining the age at which to begin mammography screening because any recommendations incorporating breast density will need an initial mammogram to determine the density, yet the starting age of screening mammography hinges on guideline recommendations. For example, the latest breast cancer screening guidelines for average-risk women from the U.S. Preventive Services Task Force (USPSTF) recommend biennial mammography screening for women between 50 and 74 years of age (grade B) but leave the screening decision to personal preference for women in their 40s (4). Outside the United States, the United Kingdom's National Health Service (NHS) invites eligible women to breast cancer screening every 3 years starting at age 50 years (5). Women following either of these recommendations will have no knowledge of their breast density until their first mammogram at 50 years of age, which raises the question of whether knowing their breast density in their 40s could lead to better outcomes.

Recognizing that appropriate screening strategies may differ by breast density, we investigated the cost effectiveness of a stratified strategy that conducts baseline mammography screening at age 40 years among women at average risk for breast cancer. Information about breast density from this screen is used to allocate women with dense breasts to more intensive screening and women with nondense breasts to less intensive screening. This stratified screening strategy is compared against guideline-based, nonstratified screening strategies in terms of cost-effectiveness.

Methods

This study received exemption from the institutional review board at The University of Texas MD Anderson Cancer Center.

Model Overview and Screening Strategies

Updating a previously published and validated microsimulation model written in R statistical software, we compared 7 screening strategies (6). We defined women with dense breasts as those with heterogeneously and extremely dense breasts (BI-RADS categories C and D). All screening strategies ended after age 75 years. The strategies were 1) no screening; 2) triennial mammography from age 50 to 75 years (T50), similar to the recommendation of the NHS; 3) biennial mammography from age 50 to 75 years (B50), similar to the grade B recommendation of the USPSTF; 4) stratified annual mammography from age 50 to 75 years for women with dense breasts at age 50 years and triennial mammography from age 50 to 75 years for those without dense breasts at age 50 years (SA50T50); 5) stratified annual mammography from age 50 to 75 years for women with dense breasts at age 50 years and biennial mammography from age 50 to 75 years for those without dense breasts at age 50 years (SA50B50); 6) stratified annual mammography from age 40 to 75 years for women with dense breasts at age 40 years and triennial mammography from age 50 to 75 years for those without dense breasts at age 40 years (SA40T50); and 7) stratified annual

mammography from age 40 to 75 years for women with dense breasts at age 40 years and biennial mammography from age 50 to 75 years for those without dense breasts at age 40 years (SA40B50).

Figure 1 shows the screening strategies and an overview of the model structure. The model generated the lifetime natural histories of a hypothetical birth cohort of 500 000 women born in 1970 who were at average risk for breast cancer (no known genetic risk factors or family history of breast cancer) and whose breast cancer incidence was calibrated to match age-specific incidence in 2017 (7). For women who developed breast cancer, the model included 4 states of breast cancer disease progression: cancer-free, asymptomatic or preclinical screening-detectable cancer, symptomatic or clinical cancer, and death due to either breast cancer or competing risks. Age-specific preclinical breast cancer incidence was derived from previously published preclinical sojourn time distributions and age-specific clinical breast cancer incidence (8). “Sojourn time” is the time from when a tumor is asymptomatic but screen-detectable to when it becomes symptomatic or is diagnosed clinically (9); it determines the interval when cancer can be detected through screening. The model also incorporated estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2) status at diagnosis to determine receipt of hormonal therapy or trastuzumab. For women diagnosed with breast cancer, we predicted survival times after diagnosis depending on their age and tumor characteristics at detection, and treatment. Detailed information on the natural history model and the associated statistical methods has been published elsewhere and is summarized in the Appendix (available at [Annals.org](https://annals.org)) (6, 10–12). For the natural history of women with dense breasts, we increased the risk for preclinical breast cancer incidence, and we decreased this risk for breast cancer for women without dense breasts (13). We applied different sensitivities for mammographic screening for women in each density group. To estimate the overall effect of population screening strategies, we weighted outcomes by the proportion of women with and those without dense breasts. Finally, we applied a higher weight to women in their 40s than those aged 50 years or older (0.60 versus 0.47) to reflect the higher prevalence of dense breasts among younger premenopausal women (13).

Clinical Parameters

Table 1 summarizes the model input parameters. We obtained the prevalence of dense breasts and other clinical parameters from the literature on statistical modeling (3, 13). To capture the masking effect of high breast density, we modeled lower sensitivity for women with dense breasts than those without (13). We modeled clinical benefit of breast cancer treatments as relative reductions in the hazards of breast cancer–specific death, with hazards estimated from a multivariable survival model using data combined from 3 Cancer and Leukemia Group B trials (26–28). If a woman’s simulated estimated breast cancer survival time was shorter than her simulated natural lifetime, her death was considered to be due to breast cancer and otherwise to be due to competing causes.

Costs and Quality-Adjusted Life-Years

The model calculated cumulative lifetime medical costs of breast cancer screening and treatment from the screening starting age and estimated productivity loss from premature

death caused by breast cancer. Medical costs included costs of screening mammography, work-up procedures, cancer treatments for those diagnosed with breast cancer, and end-of-life care stratified by cause of death. The model included diagnostic mammography as the initial work-up subsequent to an abnormal finding from screening mammography, and a possible biopsy for those needing further confirmation. If a woman had a symptomatically detected tumor, her disease status would also be confirmed with diagnostic mammography and a breast biopsy. We obtained costs of screening examinations and work-up from the Physician Fee Schedule and the literature (21, 22) and analyzed Surveillance, Epidemiology, and End Results–Medicare data to estimate medical costs of treatments and end-of-life care. We estimated treatment costs related to cancer by using the difference in mean costs between patients with breast cancer and their age- and race-matched noncancer controls (Appendix Table 1, available at [Annals.org](https://www.annals.org)) (29) and obtained treatment patterns by cancer stage and age group from the National Cancer Database Public Benchmark Reports (Appendix Table 2, available at [Annals.org](https://www.annals.org)) (30). Appendix Table 1 summarizes cost by treatment patterns, cancer stages, and phase of care based on Medicare payment; the Appendix describes the costing process and the estimation of costs related to breast cancer treatments. We assumed that women retire at age 65 years, and if a woman died of breast cancer before reaching age 65 years, we estimated lost labor market earnings between the age of breast cancer death to 65 years by using age-specific wage rates for female workers in the U.S. labor market (31). All costs were inflated to 2020 U.S. dollars by using the medical care component of the Consumer Price Index. Information on loss of quality of life (health utilities) associated with breast cancer treatments and for the last 3 months of life and disutility from screening and diagnostic work-ups was obtained from the literature (16, 19, 20).

Cost-Effectiveness Analysis

We conducted cost-effectiveness analysis (CEA) from the societal perspective, as recommended by the Second Panel on Cost-Effectiveness (32). Calculation of cumulative costs and quality-adjusted life-years (QALYs) for all strategies began at age 40 years—the earliest age to start mammographic screening. We simulated a birth cohort of 500 000 women for deterministic CEA and reported findings as incremental cost-effectiveness ratios (ICERs) (33). We applied a 3% annual discount rate to costs and QALYs. We included 3 deterministic sensitivity analyses. The first analysis explored the effect of disutility associated with screening and diagnostic work-ups (20). The second analysis reduced the specificity of screening mammography by 8% to facilitate cross-model validation with similar studies published by the Cancer Intervention and Surveillance Modeling Network (CISNET) (34, 35) modeling group. This was because the age-specific screening specificity in our model was derived from the values reported in a systematic review article (14) and was roughly 8% higher than those in the CISNET models. The third analysis investigated the effect of using a birth cohort from 1960 to better understand how life expectancy in different birth cohorts affected the effectiveness and cost-effectiveness of screening. For probabilistic CEA, we ran 100 repetitions of microsimulation with a cohort size of 100 000 women each. We constructed the net benefit of each strategy S_i , defined as $(QALY_{S_i} \times \text{societal willingness-to-pay (WTP)} - \text{COST}_{S_i})$. We then calculated the probability of each strategy being the optimal strategy (that is, having the highest expected net benefit) corresponding to

a specific level of societal WTP and presented findings as the cost-effectiveness acceptability curve (33).

Role of the Funding Source

The National Cancer Institute funded this research but had no role in the design or conduct of the study, analysis or interpretation of the data, review or approval of the manuscript, or the decision to submit the manuscript for publication.

Results

Clinical Outcomes

Table 2 shows the relevant outcomes per 1000 women for 6 screening strategies compared with no screening for the base-case and sensitivity analyses. The average number of screening sessions with mammography in a woman's lifetime increased from 7040 per 1000 women for the strategy with the least frequent screening schedule (triennial screening from age 50 to 75 years [T50]) to 22 350 for the strategy with the most intensive screening schedule (stratified annual screening from age 40 to 75 years in those with dense breasts and biennial screening from age 50 to 75 years in those without dense breasts [SA40B50]). Compared with no screening, screening reduced breast cancer deaths by 8.6 per 1000 women (T50) to 13.2 per 1000 women (SA40B50) and increased discounted QALYs in the range of 25.31 per 1000 women (T50) to 43.90 per 1000 women (SA40B50). Harms included false-positive results, benign breast biopsies, and overdiagnosed cases. "Overdiagnosis" was defined as cases that would not have been clinically diagnosed if screening had not been done (for example, indolent ductal carcinoma in situ or non-breast cancer death occurring before symptom onset). The average number of false-positive screens increased from 141.2 per 1000 women for T50 to 567.3 per 1000 women for SA40B50, with benign breast biopsies per 1000 women increasing from 15.0 to 60, respectively, and the rate of overdiagnosis from 12.5% to 18.6%. Sensitivity analysis showed that the number of false-positive screens and benign breast biopsies increased as the value of specificity for screening mammography decreased.

Deterministic CEA

In the base-case analysis (Figure 2), biennial screening between age 50 and 75 (B50) was cost-effective (ICER, ≈\$22 300 per QALY) compared with T50. However, SA40B50 was incrementally cost-effective and optimal compared with the biennial strategy (ICER, ≈\$36 200 per QALY). Findings from the base-case analysis remained robust in sensitivity analyses (Figure 2) and were superior to current recommendations by the USPSTF (B50) and the NHS (T50).

Probabilistic CEA

When we accounted for the uncertainty in all parameters (Figure 3) with a societal WTP of \$100 000 per QALY, the cost-effectiveness acceptability curves showed the likelihood of each strategy being optimal with a 0.56 probability for SA40B50, a 0.38 probability for SA40T50, and a 0.02 probability for B50.

Discussion

We evaluated the cost-effectiveness of breast cancer screening strategies for starting ages of 40 and 50 years and at fixed intervals or risk-based intervals from the initial breast density classification. Because mammography is the most commonly used breast imaging modality to quantify a woman's breast density, the woman's age at the time of the first screen becomes critically important, because women with dense breasts may benefit from starting screening at an earlier age (owing to their higher risk for cancer) and having a shorter screening interval (owing to the lower sensitivity of mammography in women with dense breasts). Our study explicitly examines the projected effect of baseline mammography screening at age 40 or 50 years, extending prior research focusing on baseline screening at age 50 years (34). Findings from this research should help inform clinicians, patients, and policymakers as they weigh the potential role of breast density in making decisions regarding breast cancer screening. Our analysis suggests that a baseline breast density assessment at age 40 years, followed by annual screening for women with dense breasts and biennial screening starting at age 50 for women without dense breasts, is likely to be cost-effective. Compared with other screening strategies examined in our study, this strategy is associated with the greatest reduction in breast cancer mortality and is cost-effective but involves the most screening mammograms in a woman's lifetime and higher rates of false-positive results and overdiagnosis.

Biomedical science has advanced our understanding of breast cancer and its subtypes and risk factors. Researchers have been advocating a paradigm shift in breast cancer screening practices, moving from one-size-fits-all to risk-based screening strategies (36, 37). Comparing the performance of age-based versus risk-based screening strategies in a Swedish case-control study, Darabi and colleagues (38) found that the risk-based approach that incorporated breast density, genetic risk, and other clinical risk factors identified 10% more cases than the age-based approach. Pashayan and associates (36) compared age-based and risk-based screening strategies by using a hypothetical cohort of women in the United Kingdom and concluded that risk-based strategies were likely to be more cost-effective than age-based strategies. In a modeling study of a Spanish population, Vilapriño and coworkers (39) examined more than 2600 screening strategies in 4 risk groups, with risk determined by breast density, family history of breast cancer, and personal history of biopsy. They concluded that risk-based strategies had fewer harms and lower costs than age-based strategies. Although these studies documented the benefit of risk-based screening over age-based screening, the actual implementation of risk-based screening strategies can be daunting because of the large number of plausible strategies based on combining a multitude of risk factors, some of which are not easily assessed at a population level.

Incorporating density information in the design and implementation of population-based cancer screening strategies is a clinically feasible form of risk-based screening. Indeed, the masking effect of dense breasts on mammography has prompted some researchers to advocate for screening strategies stratified by breast density (34, 40). Using 3 models from CISNET for women aged 50 years or older, Trentham-Dietz and colleagues (34) suggested triennial screening for average-risk women with low breast density and annual screening for higher-risk women with high breast density. We also examined this strategy and found that

this strategy (SA50T50) was a less efficient use of resources (by “extended dominance”) relative to stratified breast density–based screening at age 40 years (SA40B50). The comparison of the relative outcomes of strategy B50 from our sensitivity analysis that reduced screening mammography specificity by 8% with those from the same strategy reported by Mandelblatt and associates (35) offers an opportunity for cross-model validation, because their study also focused on average-risk women and incorporated breast density. Although our estimated number of benign biopsies was slightly lower (112.5 per 1000 women) than the range reported in their study (120 to 205 per 1000 women), which was probably driven by a stricter algorithm of receiving breast biopsies applied in our model (that is, positive diagnostic mammography after positive screening mammography), the false-positive screens, overdiagnosed cases, and rate of overdiagnosis estimated from our model were within the range reported in their study (996.7 versus 803 to 1325 per 1000 women; 14.9 versus 11 to 34 per 1000 women; and 12.7% versus 8% to 22%, respectively).

Baseline screening at age 40 years offers an opportunity to gather information on breast density, which can then be used to facilitate patient–physician communication and determine the best way forward. This baseline assessment can be expanded to collect other information, such as family history or polygenic risk scores (41), to further develop a risk profile that allows more targeted and personalized screening. Baseline screening at age 40 years also offers a “teachable moment” to educate women about breast density and discuss preventive strategies (such as more frequent screening or lifestyle modifications) to mitigate breast cancer risk. Knowledge gained from these discussions can potentially alleviate women’s anxiety when receiving their breast density notification (42), which became a federal requirement on 15 February 2019 (43).

A strength of our study is that we formally addressed uncertainty associated with results from the CEAs by repeating the simulation from the same model 100 times, with 100 000 women each, in addition to incorporating uncertainty of data inputs and population heterogeneity. This approach allowed us to report the model results in terms of cost-effective acceptability curves that inform about the probability that a certain strategy is optimal at a given societal WTP (44). Some modeling studies that assess the cost-effectiveness of cancer screening strategies address uncertainty associated with the estimated ICER by reporting a range of point estimates from multiple independently developed models (45). Although such reporting reflects structural uncertainty, it does not inform decision makers about the underlying uncertainties associated with the ICER estimated from each model. Given that many models of breast cancer screening have found screening to yield a small incremental benefit at population level, characterization of the uncertainties of cost-effectiveness estimates becomes even more important because the small magnitude of incremental benefit translates into a small denominator for the ICER, which then causes a wide variation in ICER.

Our study has limitations. First, our model did not examine alternative screening modalities for women with dense breasts. Prior research has shown that for women with dense breasts, digital breast tomosynthesis combined with digital mammography is more cost-effective than digital mammography alone (46). Although we expected the baseline screening strategy at age 40 years to become more effective if our model added tomosynthesis for women with

high breast density, augmenting digital mammography with tomosynthesis would also increase the cost of screening, particularly annual screening. Therefore, future research should explore the implication of newer screening modalities on the cost-effectiveness of the proposed stratified screening strategy. In addition, although breast density changes with age (47), we modeled women's breast density classification as static on the basis of density at the baseline screening, other than differentiating the prevalence of dense breasts for women younger than 50 years and those aged 50 years or older. The relationship among mammographic density, age, and breast cancer incidence is complex. Although high density and older age are both associated with a higher risk for breast cancer (48, 49), breast density generally decreases with age. The natural history for women with dense breasts may also differ from those without dense breasts. We did not explicitly incorporate these potential differences into our model because of the lack of reliable information on these input parameters in the current literature. Nevertheless, if women with high breast density also have shorter sojourn times, they will be likely to benefit more from shorter screening intervals, and our proposed screening strategy would probably be even more cost-effective compared with other evaluated strategies. Future studies that model breast density dynamically could explore a modified version of our stratified strategy that reassesses breast density classification at age 50 years and switches their screening interval from annual to biennial if warranted at that time.

In conclusion, current knowledge of the effect of breast density on the breast cancer screening, diagnosis, and disease progress emphasizes the importance of incorporating breast density information in the design and implementation of population-based cancer screening strategies. Yet, breast density classification is largely determined by mammography, making the timing of the first screening mammogram critical. Our analysis suggests that a baseline breast density assessment at age 40 years, followed by an annual screening for women with dense breasts and biennial screening starting at age 50 years for women without dense breasts, is likely to be cost effective and warrants consideration by national panels developing early detection recommendations for breast cancer screening.

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Appendix:: Model Description, Validation, and Costing Process

Natural History Model

Our cost-effectiveness analysis built upon a previously published national history microsimulation model for women at average risk for breast cancer. The microsimulation model was initially designed to describe the natural history of breast cancer and to capture how the disease history would be modified by screening practices and subsequent treatments (10, 12). Appendix Figure 1 shows the structure of the microsimulation model.

Using Monte Carlo simulation, the model simulated the natural history of breast cancer throughout lifetime for each woman in a large birth cohort of women. We applied statistical methods to estimate preclinical age-specific breast cancer incidence, sojourn time distribution (the period during which a tumor is asymptomatic but screen-detectable and ends at symptomatic or clinical diagnosis), tumor growth, survival, and age- and tumor size-dependent screening sensitivity, and we incorporated separate hazards rates for the effect of various cancer treatments. We estimated preclinical age-specific breast cancer incidence from the sojourn time distribution and observed age-specific incidence because preclinical age-specific incidence cannot be directly observed. A random preclinical sojourn time was generated for each woman depending on her age at onset of preclinical disease, with uncertainty incorporated through an inverse gamma prior probability distribution for the mean sojourn time using parameters that match the estimated means and SDs from the breast cancer screening trials (8). For screening mammography, we used a β distribution to reflect a random variation in screen sensitivity while matching the corresponding age- and density-specific mean sensitivity for digital mammography. For women diagnosed with breast cancer, we employed the exponential tumor growth model to model tumor volume doubling time (50). We predicted the number of nodes at diagnosis by using a Poisson linear model, given age and tumor size from the SEER data. We simulated hormonal status and HER2 status independently and determined stage of disease by using the tumor-node-metastasis staging system, given tumor size and the predicted number of nodes (51). Specific adjuvant treatment by molecular subtype was offered accordingly to the patterns of treatment.

On the basis of the natural history of breast cancer, women were classified into 2 groups: those who would never have breast cancer (the “healthy” cohort) and those who would eventually develop breast cancer before death. For the latter group and in the scenario where screening was implemented, their cancer could be detected through screening while the disease was still in preclinical state. If the cancer was missed by screening, it could become symptomatic and be detected clinically. Some women in this group might never have had their cancer detected before they died of other causes. In the scenario with no screening, breast cancer would only be detected clinically. Once a cancer was detected, the patient’s stage at diagnosis fell into 1 of 5 cancer stages on the basis of her tumor characteristics: ductal carcinoma in situ/stage 0 or stage I to IV. The survival model given her age at diagnosis, tumor characteristics, and treatments was then applied to simulate the woman’s time of breast cancer death as well as her time of death from other causes; whichever occurred first was recorded as her time and cause of death. “Overdiagnosis” was defined as cases that would not have been clinically diagnosed without screening owing to the indolent nature of tumor or non-breast cancer death that occurred before symptom diagnosis. Estimation details of the statistical methods can be found elsewhere (12).

Model Validations

We performed 2 model validations. First, to ensure the model accurately captured the natural history of breast cancer, we started from the “no screening” scenario, because it reflected the natural history of the disease. We calibrated model parameters related to breast cancer incidence against the age-specific incidence observed in the SEER registry (52) in the era

before screening mammography was widely adopted in clinical practice (53). We extracted the breast cancer incidence rate from SEER 1973 to 1979 data and applied linear extrapolations to derive age-specific breast cancer incidence at 1-year age intervals, because cancer incidence in SEER was reported at 5-year age intervals. We then compared the age-specific breast cancer incidence rates generated from our natural history model with those obtained from the SEER 1973 to 1979 data. Appendix Figure 2 shows that the incidence rates generated from our natural history model matched well with the observed age-specific incidence in the United States.

The second validation compared breast cancer mortality estimated from our model with that observed in the SEER data. We performed this validation by first updating our model by recalibrating with breast cancer incidence in 2017, the latest incidence reported by the Centers for Disease Control and Prevention (7). We then compared breast cancer mortalities (25-year, 30-year, and lifetime) with mortality observed in SEER, obtained from the current version of DevCan software (54). Validation of model-based breast cancer mortality against that observed from SEER was much more complicated than validation against breast cancer incidence, because many factors affected breast cancer mortality, such as screening strategies, treatment modalities, and adherence to screening as well as treatment guidelines; this made it extremely challenging to precisely match the mortality predicted from simulation models, which often assumed 100% adherence to screening. Our validation of mortality compared SEER mortality with breast cancer mortalities predicted from the most intensive screening strategy (annual screening from age 40 to 75 years) versus the least intensive strategy (no screening). The observed mortality should be higher than the predicted mortality of the most intensive screening strategy and lower than that of the least intensive strategy. As shown in Appendix Figure 3, the anticipated pattern is consistently found in 25-year, 30-year, and lifetime breast cancer mortality.

Incorporating Cost Information to Natural History Model

To expand the above microsimulation model for CEA, we kept track of all screening- and treatment-related clinical events in the model that would consume health care resources. Appendix Figure 1 shows how we integrated cost information into the model for CEA and assigned the relevant costs to these events. Before a confirmed diagnosis of breast cancer, the CEA model would capture costs of screening mammography as well as downstream costs (such as diagnostic mammography or biopsy) after an abnormal finding. For women with confirmed diagnosis of breast cancer, we analyzed SEER–Medicare data to estimate costs associated with breast cancer treatment by cancer stage and phase of care. Finally, we added costs associated with 5 years of hormonal therapy for women with estrogen receptor– or progesterone receptor–positive breast cancer and costs of trastuzumab for those with HER2-positive breast cancer.

Estimating Cost Related to Breast Cancer Treatment

Using SEER–Medicare data 1992–2013, we applied the phase-of-care costing approach to categorize costs of breast cancer treatment into 3 care phases: initial, continuing, and terminal care (30, 55). The initial care phase was defined as the first 12 months after cancer

DCIS = ductal carcinoma in situ; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; PR = progesterone receptor.

Appendix Figure 2. Observed versus predicted age-specific breast cancer incidence.
SEER = Surveillance, Epidemiology, and End Results.

Appendix Figure 3. Observed versus predicted breast cancer mortality.
SEER = Surveillance, Epidemiology, and End Results.

Appendix Table 1.

Annual Costs of Breast Cancer Treatment

Care Phase	Cost, \$*				
	Stage 0	Stage I	Stage II	Stage III	Stage IV
Initial care					
No chemotherapy, no radiation therapy, no surgery	0	785	9113	15 486	26 113
No chemotherapy, no radiation therapy, lumpectomy	4157	9113	12 761	18 352	30 762
No chemotherapy, no radiation therapy, mastectomy	12 280	13 898	17 860	25 313	36 303
No chemotherapy, radiation therapy, no surgery	6294	5691	12 385	27 358	47 195
No chemotherapy, radiation therapy, lumpectomy	17 743	21 687	24 744	31 165	41 334
No chemotherapy, radiation therapy, mastectomy	22 453	23 915	30 556	35 251	44 554
Chemotherapy, no radiation therapy, no surgery	8835	8601	32 275	36 963	62 283
Chemotherapy, no radiation therapy, lumpectomy	12 477	32 527	39 995	62 600	81 516
Chemotherapy, no radiation therapy, mastectomy	29 704	41 795	46 545	60 198	71 324
Chemotherapy, radiation therapy, no surgery	22 535	36 628	44 185	62 488	88 280
Chemotherapy, radiation therapy, lumpectomy	20 965	48 702	55 927	66 301	73 660
Chemotherapy, radiation therapy, mastectomy	29 607	58 349	63 137	70 668	82 982
Continuing care					
Year 1	0	1442	3873	9489	26 419
Year 2	0	879	2574	6465	23 618
Year 3	0	848	2436	6097	22 746
Year 4	0	1071	2767	4853	20 059
Year 5	0	759	2032	3409	14 815
Year 6	0	724	1257	3368	15 260
Terminal care					
Cause of death: breast cancer	71 196	81 413	87 209	97 351	120 192
Cause of death: other	12 462	5554	8889	19 944	53 062

* In 2020 U.S. dollars.

Appendix Table 2.

Breast Cancer Treatment Patterns

Age and Treatment Pattern	Utilization, %				
	Stage 0	Stage I	Stage II	Stage III	Stage IV
Age <70 y					
No chemotherapy, no radiation therapy, no surgery	2.7	1.2	1.2	1.0	11.2
No chemotherapy, no radiation therapy, lumpectomy	34.7	16.9	6.8	1.3	6.4
No chemotherapy, no radiation therapy, mastectomy	17.3	8.1	7.0	4.4	0.0
No chemotherapy, radiation therapy, no surgery	0.2	0.1	0.1	0.1	10.6
No chemotherapy, radiation therapy, lumpectomy	27.9	29.2	5.1	0.5	4.1
No chemotherapy, radiation therapy, mastectomy	13.9	14.0	5.3	1.9	0.0
Chemotherapy, no radiation therapy, no surgery	0.1	0.2	1.3	3.3	30.1
Chemotherapy, no radiation therapy, lumpectomy	1.1	7.7	13.6	4.1	15.2
Chemotherapy, no radiation therapy, mastectomy	0.6	3.7	14.1	14.1	0.0
Chemotherapy, radiation therapy, no surgery	0.0	0.0	0.2	0.7	8.0
Chemotherapy, radiation therapy, lumpectomy	1.0	12.8	22.3	15.5	14.4
Chemotherapy, radiation therapy, mastectomy	0.5	6.1	23.1	53.1	0.0
Age 70 y					
No chemotherapy, no radiation therapy, no surgery	3.4	1.7	2.4	3.4	27.9
No chemotherapy, no radiation therapy, lumpectomy	42.1	33.9	22.6	6.1	14.9
No chemotherapy, no radiation therapy, mastectomy	15.6	12.9	24.1	22.8	0.0
No chemotherapy, radiation therapy, no surgery	0.3	0.1	0.2	1.3	16.4
No chemotherapy, radiation therapy, lumpectomy	27.5	32.7	13.4	4.1	6.4
No chemotherapy, radiation therapy, mastectomy	10.2	12.4	14.3	15.4	0.0
Chemotherapy, no radiation therapy, no surgery	0.1	0.1	0.6	2.7	18.4
Chemotherapy, no radiation therapy, lumpectomy	0.4	1.9	5.2	2.9	8.0
Chemotherapy, no radiation therapy, mastectomy	0.1	0.7	5.5	11.0	0.0
Chemotherapy, radiation therapy, no surgery	0.0	0.0	0.1	0.5	3.4
Chemotherapy, radiation therapy, lumpectomy	0.3	2.5	5.7	6.3	4.6
Chemotherapy, radiation therapy, mastectomy	0.1	1.0	6.1	23.7	0.0

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Figure 1. Flow diagram of the microsimulation model and the 7 screening strategies.

B50 = biennial mammography from age 50 to 75 years; SA40B50 = stratified annual mammography from age 40 to 75 years for women with dense breasts at age 40 years and biennial mammography from age 50 to 75 years for those without dense breasts at age 40 years; SA40T50 = stratified annual mammography from age 40 to 75 years for women with dense breasts at age 40 years and triennial mammography from age 50 to 75 years for those without dense breasts at age 40 years; SA50B50 = stratified annual mammography from age 50 to 75 years for women with dense breasts at age 50 years and biennial mammography

from age 50 to 75 years for those without dense breasts at age 50 years; SA50T50 = stratified annual mammography from age 50 to 75 years for women with dense breasts at age 50 years and triennial mammography from age 50 to 75 years for those without dense breasts at age 50 years; T50 = triennial mammography from age 50 to 75 years.

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Figure 2. Cost-effectiveness frontier.

Discounted lifetime cost versus discounted quality-adjusted life-years for each screening strategy for the base-case scenario (1970 birth cohort) (A) and 3 sensitivity analyses. The screening strategies in boxes are those along the cost-effectiveness frontier (*solid line*) for which ICERs were compared; strategies above the solid line were dominated (more expensive and less effective than the alternative comparator along the frontier) or extendedly dominated (a less efficient use of resources than the alternative comparator). B50 = biennial mammography from age 50 to 75 years; ICER = incremental cost-effectiveness ratio; SA40B50 = stratified annual mammography from age 40 to 75 years for women with dense breasts at age 40 years and biennial mammography from age 50 to 75 years for those without dense breasts at age 40 years; SA40T50 = stratified annual mammography from age 40 to 75 years for women with dense breasts at age 40 years and triennial mammography from age 50 to 75 years for those without dense breasts at age 40 years; SA50B50 = stratified annual mammography from age 50 to 75 years for women with dense breasts at age 50 years and biennial mammography from age 50 to 75 years for those without dense breasts at age 50 years; SA50T50 = stratified annual mammography from age 50 to 75 years for women with dense breasts at age 50 years and triennial mammography from age 50 to 75 years for those without dense breasts at age 50 years; T50 = triennial mammography from age 50 to 75 years.

Figure 3. Cost-effectiveness acceptability analysis.

The cost-effectiveness acceptability curve plots the probability that a strategy is optimal (that is, yields the highest net benefit compared with other competing strategies) or, in other words, cost-effective at each societal willingness-to-pay threshold. Using a societal willingness-to-pay threshold of \$100,000 per quality-adjusted life-year, the probability of screening strategy SA40B50 being optimal was 56% and the probability of strategy SA40T50 being optimal was 38%. None of the remaining 5 screening strategies had more than a 3% chance of being the optimal screening strategy. B50 = biennial mammography from age 50 to 75 years; ICER = incremental cost-effectiveness ratio; SA40B50 = stratified annual mammography from age 40 to 75 years for women with dense breasts at age 40 years and biennial mammography from age 50 to 75 years for those without dense breasts at age 40 years; SA40T50 = stratified annual mammography from age 40 to 75 years for women with dense breasts at age 40 years and triennial mammography from age 50 to 75 years for those without dense breasts at age 40 years; SA50B50 = stratified annual mammography from age 50 to 75 years for women with dense breasts at age 50 years and biennial mammography from age 50 to 75 years for those without dense breasts at age 50 years; SA50T50 = stratified annual mammography from age 50 to 75 years for women with dense breasts at age 50 years and triennial mammography from age 50 to 75 years for those without dense breasts at age 50 years; T50 = triennial mammography from age 50 to 75 years.

Table 1.

Model Inputs: Clinical and Cost Parameters*

Parameter	Value	Data Source
Clinical		
Age-specific incidence in an average-risk cohort	0.12%–0.42%	Reference 7
Risk for breast cancer relative to average risk		
Age 40–49 y	Dense breasts: 1.23 Nondense breasts: 0.67	Reference 13
Age 50–64 y	Dense breasts: 1.29 Nondense breasts: 0.79	Reference 13
Age 65–74 y	Dense breasts: 1.30 Nondense breasts: 0.87	Reference 13
Prevalence		
Age 40–49 y	Dense breasts: 60% Nondense breasts: 40%	Reference 13
Age 50 y	Dense breasts: 47% Nondense breasts: 53%	Reference 13
Mean sojourn time (SD)		
Age 50 y	1.9 y (1.2)	Reference 8
Age >50 y	3.1 y (0.94)	Reference 8
Performance characteristics		
Sensitivity of digital mammography (age- and density-dependent)		
Age 40–49 y	Dense breasts: 0.801 Nondense breasts: 0.897	Reference 13
Age 50–64 y	Dense breasts: 0.868 Nondense breasts: 0.933	Reference 13
Age 65 y	Dense breasts: 0.905 Nondense breasts: 0.953	Reference 13
Mammography specificity (age-dependent)	0.922–0.995	Reference 14
Diagnostic mammography sensitivity	0.88	Reference 15
Diagnostic mammography specificity	0.900	Reference 15
Hazard ratio of breast cancer mortality		
Hormonal therapy, ER/PR-positive breast cancer	0.67	References 16, 17
Trastuzumab, HER2-positive breast cancer	0.66	References 16, 18

Parameter	Value	Data Source
Health utility value (associated time duration)		
Surgery	0.87 (3 mo)	References 16, 19
Radiation therapy	0.80 (3 mo)	References 16, 19
Chemotherapy	0.74 (1 y)	References 16, 19
Hormonal therapy with tamoxifen	0.99 (5 y)	References 16, 19
Terminal stage, breast cancer	0.29 (last 3 mo of life)	References 16, 19
Terminal stage, other diseases	0.375 (last 3 mo of life)	References 16, 19
Health utility decrement (disutility) of screening and workgroup (associated time duration)		
Screening mammography	0.006 (7 d)	Reference 20
Diagnostic work-up	0.105 (35 d)	Reference 20
Cost		
Screening-related		
Mammography (digital, bilateral)	\$139	Reference 21
Diagnostic mammography (digital, unilateral)	\$172	Reference 21
Breast biopsy	\$943.12	Reference 21, 22
Treatment-related		
Tamoxifen for 5 y	\$1400	Reference 23
Trastuzumab [†]		
As adjuvant therapy per year	\$79 184	Reference 24
For metastatic breast cancer	\$45 717	Reference 24; 4.3% mark-up
Annual costs by phase and stage	Appendix Table 1	Researchers' own analysis of SEER–Medicare data (25)

ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; PR = progesterone receptor; SEER = Surveillance, Epidemiology, and End Results.

^{*} Cost parameters are in 2020 U.S. dollars. Random variation is added according to a β distribution for all sensitivity and specificity estimates. Several parameters are presented as ranges because the sensitivity and specificity of screening mammography depend on the tumor size and the patient's age.

[†] Calculated on the basis of the dosage for an average patient who is 170 cm tall and weighs 70 kg. We used the average sales price plus 6% mark-up for an initial dose of 4 mg/kg administered via a 90-minute intravenous infusion, then 2 mg/kg administered via a 30-minute intravenous infusion weekly, for 52 weeks for adjuvant breast cancer and 7.4 months for metastatic breast cancer.

Table 2.

Results of Deterministic Analyses, Base-Case Analysis, and Sensitivity Analyses

Analysis and Screening Strategy	Average Value per 1000 Women Screened (Versus No Screening)								
	Mammography Screening Sessions, <i>n</i>	Breast Cancer Deaths Averted With Screening, <i>n</i>	FalsePositive Screens, <i>n</i>	Benign Breast Biopsies With Screening, <i>n</i>	Overdiagnosed Cases With Screening, <i>n</i>	Overdiagnosed Cases With Screening, %	Additional Costs Versus No Screening, \$*	Additional Life-Years Versus No Screening*	Additional QALYs Versus No Screening*
Base case: 1970 birth cohort	No screening	0	34,492	0	0	—	8 176 000	19 624	19 607
	T50	7040	8.6	141.2	15.0	12.5	24 000	25.50	25.31
	B50	10 190	10.2	202.5	22.0	14.7	101 000	29.00	28.80
	SA50T50	13 180	10.7	259.3	28.0	15.7	344 000	30.78	30.57
	SA50B50	14 850	11.4	292.1	31.0	16.9	374 000	32.18	31.98
	SA40T50	21 090	12.5	542.2	58.0	17.8	601 000	41.38	41.15
	SA40B50	22 350	13.2	567.3	60.0	18.6	648 000	44.11	43.90
	Sensitivity analyses	Disutility associated with screening mammography and diagnostic work-up							
No screening		0	34,492	0	0	—	8 176 000	19 624	19 606
T50		7040	8.6	141.2	15.0	12.5	24 000	25.50	23.33
B50		10 190	10.2	202.5	22.0	14.7	101 000	29.00	25.98
SA50T50		13 180	10.7	259.3	28.0	15.7	344 000	30.78	26.99
SA50B50		14 850	11.4	292.1	31.0	16.9	374 000	32.18	27.95
SA40T50		21 090	12.5	542.2	58.0	17.8	601 000	41.38	34.38
SA40B50		22 350	13.2	567.3	60.0	18.6	648 000	44.11	36.79
8% reduction in the specificity of screening mammography									
No screening	0	34,19	0	0	0	—	8 162 157	19 624	19 607
T50	7591	8.5	689.9	78.6	12.4	10.7	58 961	25.71	25.47

Analysis and Screening Strategy	Average Value per 1000 Women Screened (Versus No Screening)								
	Mammography Screening Sessions, <i>n</i>	Breast Cancer Deaths Averted With Screening, <i>n</i>	FalsePositive Screens, <i>n</i>	Benign Breast Biopsies With Screening, <i>n</i>	Overdiagnosed Cases With Screening, <i>n</i>	Overdiagnosed Cases With Screening, %	Additional Costs Versus No Screening, \$*	Additional Life-Years Versus No Screening*	Additional QALYs Versus No Screening*
B50	10 982	10.0	996.7	112.5	14.9	12.7	274 594	32.22	31.97
SA50T50	14 211	10.5	1290.7	146.2	15.6	13.3	491 830	31.77	31.52
SA50B50	16 015	11.3	1454.0	164.4	16.9	14.3	656 904	35.02	34.73
SA40T50	22 599	12.2	2052.6	231.4	17.8	14.9	1 006 850	42.85	42.58
SA40B50	23 961	12.8	2175.9	245.2	18.7	15.6	1 006 850	44.19	43.93
1960 birth cohort									
No screening	0	33.806	0	0	0	—	8 415 000	19 061	19 044
T50	6920	8.4	138.6	14.0	12.9	10.70	13 000	20.84	20.54
B50	10 020	9.9	200.2	21.0	15.4	12.90	87 000	23.72	23.43
SA50T50	12 960	10.4	255.6	27.0	16.2	13.70	307 000	24.41	24.10
SA50B50	14 600	11.1	288.0	31.0	17.6	14.90	349 000	26.04	25.74
SA40T50	20 800	12.3	535.9	57.0	18.9	16.10	485 000	39.47	39.23
SA40B50	22 050	13.1	561.1	60.0	19.8	18.20	546 000	40.56	40.31

B50 = biennial mammography from age 50 to 75 years (without density information); QALY = quality-adjusted life-year; SA40B50 = stratified annual mammography from age 40 to 75 years for women with dense breasts at age 40 years and biennial mammography from age 50 to 75 years for those without dense breasts at age 40 years; SA40T50 = stratified annual mammography from age 40 to 75 years for women with dense breasts at age 40 years and triennial mammography from age 50 to 75 years for those without dense breasts at age 40 years; SA50B50 = stratified annual mammography from age 50 to 75 years for women with dense breasts at age 50 years and biennial mammography from age 50 to 75 years for those without dense breasts at age 50 years; SA50T50 = stratified annual mammography from age 50 to 75 years for women with dense breasts at age 50 years and triennial mammography from age 50 to 75 years for those without dense breasts at age 50 years; T50 = triennial mammography from age 50 to 75 years (without density information).

* Discounted.