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Economic Evaluation

Assessing the Cost-Effectiveness of Updated Breast Cancer Screening Guidelines for Average-Risk Women

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A B S T R A C T

Background: Several specialty societies have recently updated their breast cancer screening guidelines in late 2015/early 2016. **Objectives:** To evaluate the cost-effectiveness of US-based mammography screening guidelines. **Methods:** We developed a microsimulation model to generate the natural history of invasive breast cancer and capture how screening and treatment modified the natural course of the disease. We used the model to assess the cost-effectiveness of screening strategies, including annual screening starting at the age of 40 years, biennial screening starting at the age of 50 years, and a hybrid strategy that begins screening at the age of 45 years and transitions to biennial screening at the age of 55 years, combined with three cessation ages: 75 years, 80 years, and no upper age limit. Findings were summarized as incremental cost-effectiveness ratio (cost per quality-adjusted life-year [QALY]) and cost-effectiveness acceptability frontier. **Results:** The screening strategy that starts annual mammography at the age of 45 years and switches to biennial screening between the ages of 55 and 75 years was the most cost-effective, yielding an incremental cost-effectiveness ratio of $40,135/QALY. Probabilistic analysis showed that the hybrid strategy had the highest probability of being optimal when the societal willingness to pay was between $44,000/QALY and $103,500/QALY. Within the range of commonly accepted societal willingness to pay, no optimal strategy involved screening with a cessation age of 80 years or older. **Conclusions:** The screening strategy built on a hybrid design is the most cost-effective for average-risk women. By considering the balance between benefits and harms in forming its recommendations, this hybrid screening strategy has the potential to optimize the health care system's investment in the early detection and treatment of breast cancer.

Keywords: breast cancer screening guidelines, cost-effectiveness analysis, microsimulation models, screening mammography

Introduction

Breast cancer is the most frequently diagnosed cancer in women and the second leading cause of cancer deaths for women in the United States [1]. The estimated number of incident cases of female breast cancer in the United States for 2018 is 266,120, and it was estimated that 40,920 women in the United States would die of breast cancer in 2018 [1]. The benefit of screening mammography in cancer control has been established in clinical trials and observational and modeling studies. A systematic review published in 2015 concluded that screening mammography was associated with an approximately 20% reduction in breast cancer mortality among women at an average risk of developing breast cancer [2]. Nevertheless, growing awareness of the range of harms associated with breast cancer screening (e.g., false positives and overdiagnosis) [3] has raised interests and questions over what constitutes an optimal screening strategy that balances the harms and benefits of breast cancer screening at the population level.

In the United States, for women at an average risk of developing breast cancer, several specialty societies, including the US Preventive Services Task Force (USPSTF), the American Cancer Society (ACS), the American College of Radiology (ACR), the American Congress of Obstetricians and Gynecologists (ACOG), the American Association of Family Physicians (AAFP), and the American College of Physicians (ACP), have published breast cancer screening guidelines. Both the ACS and the USPSTF updated their breast cancer screening guidelines in late 2015/early 2016. The 2016 updated guideline from the USPSTF was similar to its recommendation in 2009 [4], but the 2015 updated ACS guideline differed substantially from its previous guideline published in 2003 [5]. Two important differences between the updated ACS breast cancer screening guideline and its 2003 guideline (which recommended annual mammography screening starting at the age of 40 years) are that 1) the recommended starting age of screening is 45 years and 2) the recommended screening interval transition from annual to biennial is after reaching the age of 55

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years. Similar to the updated USPSTF guideline, the updated ACS guideline does not suggest a specific age to stop screening; instead it offers a general guidance that mammography screening should be continued as long as a woman's overall health is good with a life expectancy of 10 years or more, leaving the decision to the discretion of women and their physicians as in the case for women aged between 40 and 44 years. The scientific rationale behind these recommendations is influenced by the quality of existing evidence and the consideration of trade-off between benefits and harms related to screening mammography [5].

The objective of our study was to use a microsimulation model to assess the cost-effectiveness of three US-based mammography screening guidelines: the updated and previous ACS guidelines and the updated USPSTF guideline. It should be noted that this comparison essentially covers guidelines from other specialty societies because the AAFP and ACP guidelines agree with the updated USPSTF guidelines, and the ACOG and ACR guidelines are similar to the previous ACS guideline that recommends annual mammography screening starting at the age of 40 years. Findings from this assessment will assist decision makers in planning, designing, and promoting efficient cancer control strategies for women at an average risk of developing breast cancer.

Methods

Natural History Model

We generated the natural histories of a large cohort of women at an average risk of developing breast cancer by incorporating ductal carcinoma in situ (DCIS) into a previously published microsimulation model for invasive breast cancer [6,7]. The statistical details for the construction of the microsimulation model can be found in the study by Shen and Parmigiani [8], and the model structure is described in the schematic diagram in the Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.07.880. Briefly, the model simulated each woman's natural history throughout her lifetime for a large cohort of women born in 1960 using Monte-Carlo simulations. For women who developed breast cancer according to their age-specific incidence [9], the model captured four states of disease progression: disease-free or asymptomatic, screen-detectable preclinical disease, clinical disease, and death due to competing risks or breast cancer. Because the ages at onset of preclinical disease are unobservable, they were derived from age-specific breast cancer incidence and the preclinical sojourn time distributions. 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 for the mean sojourn time using parameters that match the estimated means and SDs from the screening trials [10].

Of the two forms of DCIS (progressive and nonprogressive), our model focused explicitly on nonprogressive DCIS because treatments received by patients with this condition represent overdiagnosis and overtreatment. Specifically, we assumed that nonprogressive DCIS remains indolent and/or regresses to a normal state for women with this diagnosis; therefore, they would not be clinically diagnosed if the DCIS was not detected from screening mammography, nor would they die of DCIS. The progressive form of DCIS would be captured as invasive breast cancer under this modeling approach. We calibrated the percentage of nonprogressive DCIS to be about 9% using data provided by van Ravesteyn et al. [11], who reported that approximately 17% of patients with breast cancer were diagnosed with DCIS, and of those, 51.3% had nonprogressive DCIS.

We used the exponential tumor growth model to model tumor volume-doubling time [12]. Our model assumed that patients' tumor characteristics were known at the time of treatment, and we obtained a woman's tumor size at diagnosis and predicted the number of nodes at diagnosis using a Poisson linear model, given age and tumor size based on Surveillance, Epidemiology, and End Results (SEER) registry data [13]. We simulated hormonal status independently, allowing 75% to be either ER- or PR-positive [14–17] and 25% to be HER2-positive [18], and determined the stage of disease using the tumor-node-metastasis staging system, given tumor size and the predicted number of nodes [19].

Model Validation

We validated our natural history model of breast cancer with the US breast cancer incidence rate between 1973 and 1979, representing a time period in which the observed breast cancer incidence was not altered by widespread use of screening mammography [20]. We extracted the breast cancer incidence rate from SEER data for 1973 to 1979, which was reported at 5-year age intervals, and applied linear extrapolations to derive age-specific breast cancer incidence at 1-year age intervals. We calibrated model parameters related to age-specific mortality and age-specific breast cancer incidence against the age-specific incidence derived from the SEER data. Figure 1 compares the age-specific breast cancer incidence rates generated from our natural history model with those obtained from SEER data for 1973 to 1979. As shown, incidence rates generated from our calibrated natural history model match well with the observed age-specific incidence in the United States.

Modeling the Impact of Screening and Diagnostic Procedures

The clinical parameters in our model are presented in Table 1. The sensitivity of mammography increases with tumor size and age at screening, and the specificity of mammography increases with age at screening [21–26]. Building on the range of sensitivity and specificity of digital mammography reported in a recent systematic review [27], we modeled age-specific and tumor size–specific sensitivity and age-specific specificity for mammography using a logit model [26,28] and accounted for uncertainty using a beta distribution for each parameter of sensitivity and specificity. We

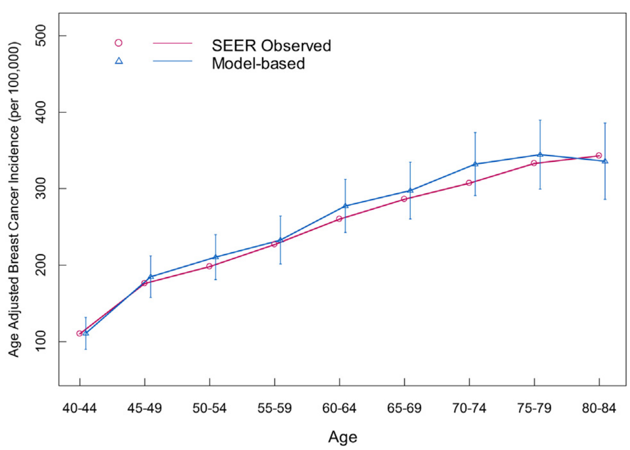

Fig. 1 – Comparison of Model-Generated Breast Cancer Incidence and Age-Specific Incidence Observed in the SEER data. Note: SEER = Surveillance, Epidemiology, and End Results. Vertical lines are 95% confidence interval of age-specific incidence estimated from the microsimulation model.

Table 1 – Model inputs: clinical and cost parameters (2017 US $).

Parameter	Values		Data source
	Clinical parameters		
Age-specific incidence	40 y ≤ age < 50 y	Age ≥50 y	Centers for Disease Control and Prevention [9]
Average risk cohort	0.12%–0.22%	0.22%–0.42%	
Sojourn time (mean ± SD)	Age ≤50 y (1.9 ± 1.2)	Age >50 y (3.1 ± 0.94)	Munoz et al. [10]
Performance characteristics			
MMG sensitivity* (age- and tumor size–dependent)	40 y ≤ age < 50 y	Age ≥50 y	Souza et al. [27]
Tumor size = 0.5 cm	0.113–0.245	0.169–0.626	
Tumor size = 1 cm	0.353–0.549	0.454–0.875	
Tumor size = 2 cm	0.881–0.961	0.917–0.998	
MMG specificity* (age-dependent)	0.922–0.967	0.968–0.995	
Diagnostic MMG sensitivity	0.88		National Cancer Institute [29]
Diagnostic MMG specificity	0.90		Sprague et al. [30]
Hazard reduction			
Hormonal therapy, ER-/PR-positive	0.67		Mariotto et al. [36]
Trastuzumab for HER2-positive	0.66		Dahabreh et al. [37]
Health utility parameters: utility value and associated duration			
Breast surgery	0.87, 3 mo		Tengs and Wallace [62]
Radiation	0.80, 3 mo		Ahern et al. [51]
Chemotherapy	0.74, 1 y		
Tamoxifen	0.99, 5 y		
Terminal stage, breast cancer	0.29, last 3 mo of life		
Terminal stage, other diseases	0.375, last 3 mo of life		
	Cost parameters		
Screening-related costs			
Mammography (digital; bilateral)	$137		Centers for Medicare & Medicaid Services [42]
Diagnostic mammography (digital; unilateral)	$167		
Breast biopsy	$831		Centers for Medicare & Medicaid Services [42] Plevritis et al. [43]
Treatment-related costs			
Tamoxifen for 5 y	$1,430		Allen [48]
Trastuzumab†			
As adjuvant therapy/y	$76,924		Centers for Medicare & Medicaid Services [50]
For metastatic breast cancer	$44,413		
Annual costs by phase and stage‡	See *Table 2*		SEER-Medicare

Note. Random variation is added using a beta distribution for all sensitivity and specificity estimates. See description under "Modeling the Impact of Screening and Diagnostic Procedures" subsection in Methods. Several parameters are presented as ranges because the sensitivity and specificity of screening mammography depend on the tumor size and/or the patient's age.

MMG, mammography; RT, radiation; SEER, Surveillance, Epidemiology, and End Results.

* Range based on the internal quartiles of sensitivity and specificity estimated from the authors' statistical models that used a beta distribution to account for uncertainty.

† Calculated on the basis of the dosage for an average patient with height 170 cm and weight 70 kg and using the average sales price plus 6% markup initial dose of 4 mg/kg over 90-min intravenous infusion, then 2 mg/kg over 30-min intravenous infusion weekly for 52 wk for adjuvant breast cancer and 7.4 mo for metastatic breast cancer [7].

‡ Authors' analysis of SEER-Medicare data.

used diagnostic mammography as the form of the initial workup for abnormal findings from screening mammography, with sensitivity and specificity estimated from the Breast Cancer Surveillance Consortium [29,30]. A biopsy was used to confirm the disease after a positive finding from the initial workup. If a woman has a symptomatically detected tumor, her disease status would also be confirmed with both diagnostic mammography and a breast biopsy. Women in the preclinical state who are never diagnosed with breast cancer are assumed to die of other causes. For women receiving false-positive mammography, a follow-up mammography is provided 6 months after the last mammography [31].

We did not make any assumptions regarding the mortality reduction of mammography screening; instead, we predicted survival times using a Cox regression model that included age, tumor characteristics at diagnosis, and treatment. Covariate coefficients on age, primary tumor size, and number of nodes at diagnosis in the baseline predictive survival model were estimated on the basis of a combined analysis of four breast cancer trials in the Cancer and Leukemia Group B cancer research cooperative group [32–35]. We then used the hazard reductions to model the additional effects on survival of treatment with tamoxifen for patients with ER- or PR-positive tumors [36] and with trastuzumab for patients with HER2-positive tumors; the magnitude of hazard reduction was 0.67 for hormonal therapies and 0.66 for trastuzumab [36,37]. If a woman's estimated breast cancer survival time was shorter than her simulated natural lifetime according to life tables for the 1960 birth cohort from the US Census Bureau, she would be assumed to have died of breast cancer; otherwise, she would die from competing risks.

Costs-Effectiveness Analysis

We integrated cost information to the aforementioned microsimulation model to assess the cost-effectiveness of various breast cancer screening strategies (see the Supplemental Materials for technical details). We performed cost-effectiveness analysis (CEA) from the societal perspective, as recommended by the US Public Health Panel on Cost-Effectiveness in Health and Medicine [38] and more recent good research practices guidelines [39–41]. For each woman, the model calculated cumulative medical costs related to breast cancer screening and treatment, estimated indirect costs in the form of productivity loss from premature death caused by breast cancer, and computed quality-adjusted life-years (QALYs) throughout her lifetime. We applied an annual discount rate of 3% to both costs and QALYs. We compared a total of 10 mammography screening strategies, including no screening and 3 cessation ages (75 years, 80 years, and no upper age limit), each associated with three guideline recommendations: annual screening interval starting at the age of 40 years (ACOG, ACR, and previous ACS guidelines), biennial screening interval starting at the age of 50 years (updated USPSTF, AAFP, and ACP guidelines), and a hybrid strategy that begins with annual screening at the age of 45 years and transitions to biennial screening at the age of 55 years (updated ACS guideline).

Medical costs captured in our model spanned from screening with digital mammography and workup procedures to breast cancer treatments and end-of-life care. Cost parameters are presented in Tables 1 and 2. Specifically, we obtained costs of screening and workup from the 2017 Physician Fee Schedule [42] and the literature [43]. We analyzed the SEER-Medicare data, covering SEER up to 2011 and Medicare up to 2013, to obtain medical costs associated with real-world treatment patterns for the incident cohort of patients with breast cancer. To obtain medical cost by treatment modality, we determined from Medicare claims whether patients had received surgery (mastectomy, lumpectomy, or none), radiation (yes/no), or chemotherapy (yes/no) within 12 months of diagnosis, and stratified by stage at diagnosis. We obtained treatment pattern by cancer stage and age group (age <70 years vs. ≥70 years) from the National Cancer Database Public Benchmark Reports [44]. Following the phase of care framework, we classified cancer care into three phases: initial, continuing, and terminal care [45]. We then applied the incremental costing approach to estimate breast cancer–related costs for each care phase using the difference in mean total medical costs between patients with breast cancer and control cohorts consisting of age- and race-matched women without cancer [46,47]. Treatment patterns (by disease stage and patient age group) and costs (by stage and phase of care) for breast cancer are presented in Table 2.

Because costs estimated from SEER-Medicare data were representative of only patients aged 65 years or older, we followed the estimation strategy in a cost report of the National Cancer Institute [45] and adjusted the SEER-Medicare estimates by a factor of 1.5 for costs in terminal care phases for patients younger than 65 years to reflect more aggressive care among young women. Furthermore, we added costs of 5-year treatment with tamoxifen [48] to 70% of patients who had ER-positive tumors [49] and costs of trastuzumab for HER2-positive tumors [50]. We estimated indirect costs (i.e., mortality costs from lost wages) using age-specific wage rates for female workers in the US labor market. All costs were normalized to 2017 US dollars.

To compute QALYs, we obtained from the literature health utilities associated with the negative effects of breast cancer treatments (i.e., surgery, radiation, chemotherapy, and hormonal therapy) and utilities for terminal disease with breast cancer versus other diseases as causes of death (Table 1) [51,52]. These utility values were weighted against their respective durations in which the treatment or disease stage applied to calculate QALYs.

We performed deterministic and probabilistic CEAs. Our simulation for deterministic CEA was based on a birth cohort of 2 million women. To address model uncertainties, we ran 100 repetitions of the simulation model with a cohort size of 100,000 women, recorded mean costs and QALYs, and constructed the net benefit of each strategy, defined as (societal willingness to pay × QALY) − cost. For deterministic CEA, we obtained the mean costs and QALYs for the simulated cohort of 2 million women, ranked the strategies by costs in ascending order, removed strategies that were dominated or extendedly dominated, and calculated the incremental cost-effectiveness ratios (ICERs) using the remaining strategies [53]. For probabilistic analysis, we calculated the probability of each strategy being the strategy with the highest expected net benefit corresponding to various levels of societal willingness to pay (e.g., $50,000/QALY or $100,000/QALY). We present findings of the probabilistic analysis in the cost-effectiveness acceptability (CEacc) frontier [53,54], which depicts the probability that the strategy with the highest net benefit is cost-effective (i.e., optimal) in corresponding to a specific level of societal willingness to pay.

This study received exemption from the Institutional Review Board at The University of Texas MD Anderson Cancer Center.

Results

Deterministic CEA

Table 3 presents the pairwise comparison of the CEA findings and summarizes the mean cost increase and QALY gain associated with each screening strategy compared with no screening. On average, screening increased the lifetime costs (discounted at 3%) for women at an average risk of developing breast cancer, ranging from $642 per person for biennial screening between the ages of 50 and 75 years to $2149 per person for annual mammography screening starting at the age of 40 years, without an upper age limit. The screening strategy that yielded the largest gain in QALYs was annual screening between ages 40 and 75 years, producing a QALY (also discounted at 3%) gain of 0.0340 per person (≈ 12.4 days) compared with no screening.

Results of stepwise comparisons from the deterministic CEA are illustrated in a cost-effectiveness plane (Fig. 2). After excluding strategies that were dominated or extendedly dominated, four strategies remained on the cost-effectiveness efficiency frontier: no screening, biennial screening 50–75, annual screening 45–54 followed by biennial screening 55–75, and annual screening 40–75; the latter three strategies represent the updated USPSTF/AAFP/ACP, updated ACS, and ACOG/ACR guidelines, respectively. The screening strategy that starts annual mammography at age 45 years and switches to biennial screening between ages 55 and 75 years was the most cost-effective. Compared with the updated USPSTF/AAFP/ACP guidelines with a cessation age of 75 years, the ICER of screening based on the updated ACS guideline was $40,135/QALY, which was below the range of the cost-effectiveness threshold ($50,000–$100,000/QALY) commonly cited in US-based cost-effectiveness studies.

Table 2 – Breast cancer treatment patterns and costs (2017 US $).

Treatment pattern	Stage 0		Stage I		Stage II		Stage III		Stage IV	
	Age <70 y	Age ≥70 y	Age <70 y	Age ≥70 y	Age <70 y	Age ≥70 y	Age <70 y	Age ≥70 y	Age <70 y	Age ≥70 y
No chemotherapy, no RT, no surgery	2.7%	3.4%	1.2%	1.7%	1.2%	2.4%	1.0%	3.4%	11.2%	27.9%
No chemotherapy, no RT, lumpectomy	34.7%	42.1%	16.9%	33.9%	6.8%	22.6%	1.3%	6.1%	6.4%	14.9%
No chemotherapy, no RT, mastectomy	17.3%	15.6%	8.1%	12.9%	7.0%	24.1%	4.4%	22.8%	0.0%	0.0%
No chemotherapy, RT, no surgery	0.2%	0.3%	0.1%	0.1%	0.1%	0.2%	0.1%	1.3%	10.6%	16.4%
No chemotherapy, RT, lumpectomy	27.9%	27.5%	29.2%	32.7%	5.1%	13.4%	0.5%	4.1%	4.1%	6.4%
No chemotherapy, RT, mastectomy	13.9%	10.2%	14.0%	12.4%	5.3%	14.3%	1.9%	15.4%	0.0%	0.0%
Chemotherapy, no RT, no surgery	0.1%	0.1%	0.2%	0.1%	1.3%	0.6%	3.3%	2.7%	30.1%	18.4%
Chemotherapy, no RT, lumpectomy	1.1%	0.4%	7.7%	1.9%	13.6%	5.2%	4.1%	2.9%	15.2%	8.0%
Chemotherapy, no RT, mastectomy	0.6%	0.1%	3.7%	0.7%	14.1%	5.5%	14.1%	11.0%	0.0%	0.0%
Chemotherapy, RT, no surgery	0.0%	0.0%	0.0%	0.0%	0.2%	0.1%	0.7%	0.5%	8.0%	3.4%
Chemotherapy, RT, lumpectomy	1.0%	0.3%	12.8%	2.5%	22.3%	5.7%	15.5%	6.3%	14.4%	4.6%
Chemotherapy, RT, mastectomy	0.5%	0.1%	6.1%	1.0%	23.1%	6.1%	53.1%	23.7%	0.0%	0.0%
Cost related to breast cancer treatment, by care phase										
Initial care phase										
No chemotherapy, no RT, no surgery	$0		$692		$8,029		$13,645		$23,009	
No chemotherapy, no RT, lumpectomy	$3,663		$8,029		$11,244		$16,170		$27,106	
No chemotherapy, no RT, mastectomy	$10,819		$12,246		$15,737		$22,304		$31,988	
No chemotherapy, RT, no surgery	$5,546		$5,015		$10,913		$24,106		$41,584	
No chemotherapy, RT, lumpectomy	$15,633		$19,110		$21,803		$27,460		$36,420	
No chemotherapy, RT, mastectomy	$19,783		$21,073		$26,923		$31,061		$39,258	
Chemotherapy, no RT, no surgery	$7,784		$7,579		$28,439		$32,568		$54,879	
Chemotherapy, no RT, lumpectomy	$10,994		$28,660		$35,240		$55,159		$71,826	
Chemotherapy, no RT, mastectomy	$26,173		$36,826		$41,012		$53,042		$62,846	
Chemotherapy, RT, no surgery	$19,856		$32,274		$38,933		$55,059		$77,786	
Chemotherapy, RT, lumpectomy	$18,473		$42,913		$49,279		$58,420		$64,904	
Chemotherapy, RT, mastectomy	$26,088		$51,413		$55,631		$62,267		$73,118	
Continuing care phase										
Year 1	$0		$1,270		$3,413		$8,361		$23,278	
Year 2	$0		$774		$2,268		$5,696		$20,811	
Year 3	$0		$747		$2,147		$5,372		$20,042	
Year 4	$0		$943		$2,438		$4,276		$17,674	
Year 5	$0		$669		$1,790		$3,004		$13,054	
Year 6+	$0		$639		$1,107		$2,968		$13,446	

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Table 2 – *continued*

Treatment pattern	Stage 0		Stage I		Stage II		Stage III		Stage IV	
	Age <70 y	Age ≥70 y	Age <70 y	Age ≥70 y	Age <70 y	Age ≥70 y	Age <70 y	Age ≥70 y	Age <70 y	Age ≥70 y
Terminal care phase										
Cause of death: breast cancer	$41,822		$47,824		$51,228		$57,186		$70,603	
Cause of death: other	$7,321		$3,263		$5,221		$11,715		$31,170	

Note. Initial care was defined as care incurred within the first 12 mo of diagnosis, terminal care reflected the last 12 mo of life, and continuing care captured everything that happens between initial and terminal care phases [45].
RT, radiation.

Probabilistic CEA

Probabilistic analysis from 100 repeated simulations is summarized as the CEacc frontier (Fig. 3). Many screening strategies never reached the CEacc frontier. Of those that are potentially the optimal screening strategies, Figure 3 shows that the updated USPSTF/AAFP/ACP recommendations (specifically, biennial screening between the ages of 50 and 75 years) are most likely optimal when the societal willingness to pay is in the range of $40,500/QALY to $44,000/QALY. The updated ACS guideline has the highest probability of being optimal when the societal willingness to pay is between $44,000/QALY and $103,500/QALY. Screening strategies involving annual screening intervals starting at the age of 40 years, as recommended by the 2003 ACS guideline and the current ACR and ACOG guidelines, are desirable only when the societal willingness to pay exceeds $103,500/QALY. Figure 2 also shows that within the wide range of societal willingness to pay explored in this study, no optimal strategy involves screening with cessation at the age of 80 years or without upper age limits.

Discussion

This study used a microsimulation model integrated with medical cost data that reflected real-world breast cancer treatment patterns to assess the cost-effectiveness of two recently updated breast cancer screening guidelines, the USPSTF and ACS guidelines, respectively, and screening strategies in the ACOG and ACR guidelines. Our findings show that screening strategies conforming to the updated ACS guideline are most likely to be cost-effective within the range of the societal willingness to pay ($50,000–$100,000/QALY) considered acceptable in the United States [55,56]. We also find that a population-based breast cancer screening program that continues screening past the age of 80 years for all women at an average risk of developing breast cancer is not cost-effective, regardless of screening intervals or initiation age.

Breast cancer remains one of the most devastating diseases for women. Although women want to guard against breast cancer through early detection from screening, as the American health care system moves toward value-based medicine, it becomes increasingly important to understand the harm-benefit trade-off of various breast cancer screening strategies. This challenge was explored in studies published by the Cancer Intervention and Surveillance Modeling Network (CISNET) [57,58]. Their recent publication used six simulation models to compare the benefits and harms of eight screening strategies, covering three starting ages (40, 45, or 50 years) in combination with annual, biennial, or a hybrid interval that transitioned from annual screening in the 40s to biennial screening at the age of 50 years, all with the same cessation age of 74 years [57]. The authors concluded that biennial strategies were the most efficient for average-risk women without further differentiating among strategies at different starting ages, because all three strategies were on the frontier of efficiency in the frontier plot [57]. Although the efficiency frontier is an informative way to illustrate the harm-benefit trade-offs because strategies not on the frontier were considered inefficient, selecting the optimal strategy from those remaining on the frontier is challenging because metrics such as life-years gained per additional

Table 3 – Costs and QALYs of breast cancer screening strategies, discounted at 3%.

Strategy, age (y)	Notation	Costs (vs. no screening)	QALYs (vs. no screening)
Updated USPSTF/AAFP/ACP breast cancer screening guidelines			
Biennial 50–75	B(50–75)	$642	0.0166
Biennial 50–80	B(50–80)	$731	0.0136
Biennial ≥50	B(50+)	$782	0.0094
Updated ACS breast cancer screening guidelines			
Annual 45–54, biennial 55–75	A(45–54) + B(55–75)	$1016	0.0260
Annual 45–54, biennial 55–80	A(45–54) + B(55–80)	$1042	0.0241
Annual 45–54, biennial ≥55	A(45–54) + B(55+)	$1069	0.0203
Previous ACS/ACOG/ACR breast cancer screening guidelines			
Annual 40–75	A(50–75)	$1942	0.0340
Annual 40–80	A(50–80)	$2050	0.0333
Annual ≥40	A(50+)	$2149	0.0282

AAFP, American Association of Family Physicians; ACOG, American Congress of Obstetricians and Gynecologists; ACP, American College of Physicians; ACR, American College of Radiology; ACS, American Cancer Society; QALY, quality-adjusted life-year; USPSTF, US Preventive Services Task Force.

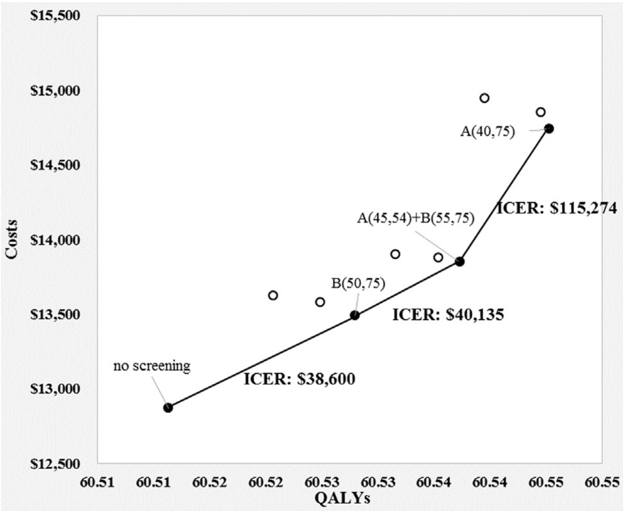

Fig. 2 – Cost-Effectiveness Plane of 10 Breast Cancer Screening Strategies. Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

mammography performed are difficult to decipher for decision makers facing budgetary constraints. By summarizing harm-benefit trade-offs in terms of cost per QALY gained, CEA offers a more transparent way to relate the harm-benefit trade-off to cost-conscious stakeholders. This exploration allows us to conclude from our model that biennial strategies considered to be efficient in the CISNET models would most likely be cost-effective only within a rather narrow range of societal willingness to pay ($40,500–$44,000/QALY).

Another important contribution of our study is that our model explored screening strategies that are based on specific guideline recommendations instead of hypothetical scenarios. This improves the practical implications of our study finding because clinicians and payers often follow guideline-recommended screening practices. As mentioned previously, two unique features of the updated ACS guideline are the starting age of screening and the hybrid interval. Although the CISNET group has explored hybrid strategies, these strategies differ from those in the updated ACS guideline in that screening transitioned to biennial intervals at the age of 50 years rather than 55 years. The transition from annual screening intervals to biennial screening intervals at the age of 55 years is an important screening strategy to consider because a recent analysis of the Breast Cancer Surveillance Consortium data showed that among pre-menopausal women, those with biennial screening intervals were more likely to have less favorable tumor characteristics (e.g., larger tumor size or tumor associated with poor prognosis at diagnosis) than those with annual screening intervals [59]. The age for transitioning from annual to biennial intervals in the updated ACS guideline was based on the rationale that most women would be postmenopausal by the age of 55 years, thus preserving the benefits of annual screening for premenopausal women [5]. Indeed, when we included transitioning at the age of 55 years in our model, the cost-effectiveness comparison favored the updated ACS guideline.

As screening technology advances, it is important that clinical parameters in modeling studies reflect the standard of care in current practice. Although the integration of digital breast tomosynthesis (also known as three-dimensional mammography) with conventional two-dimensional digital mammography has been shown to have better breast cancer detection rates and lower false-positive recalls than digital mammography alone [60], digital mammography is still considered the current standard of care for breast cancer screening among average-risk women. Therefore, our model was based on the performance characteristics of digital mammography. From a modeling perspective, it is feasible to switch from one screening modality to another over time in anticipation of digital breast tomosynthesis or another new modality eventually becoming the standard of care. Nevertheless, without solid evidence as to when the transition to a new standard of care will occur or when the performance characteristics of a potential screening modality will become available in the future,

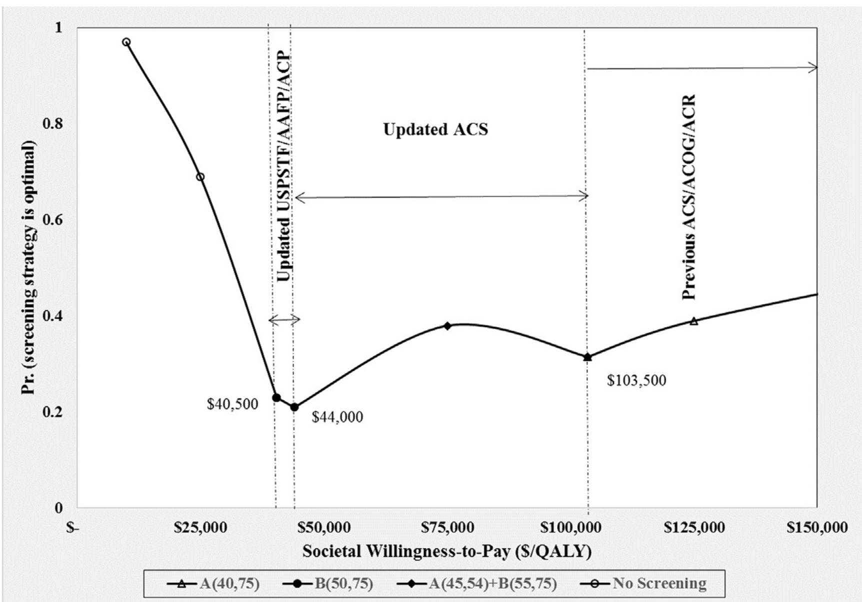

Fig. 3 – Cost-Effectiveness Acceptability Frontier of Breast Cancer Screening Strategies. Abbreviations: AAFP, American Association of Family Physicians; ACOG, American Congress of Obstetricians and Gynecologists; ACP, American College of Physicians; ACR, American College of Radiology; ACS, American Cancer Society; QALY, quality-adjusted life-year; USPSTF, US Preventive Services Task Force.

such an analysis would be highly speculative and could create major challenges for the interpretation of findings from the CEA of screening strategies that involve different initiation ages and screening intervals because of the intermixing of screening strategies and screening modalities. We use the transition from film to digital mammography to illustrate this point. Most screening facilities had replaced film mammography with digital mammography by 2010. Therefore, for the 1960 birth cohort on which our model was based, by the time the women in this cohort reached the age of 50 years, most of them would have started breast cancer screening with digital mammography. Nevertheless, for screening strategies with the initiation age of 40 years, some women in our simulation model would have started with film mammography but eventually would have been switched to digital mammography as they aged into their 50s. If we were to include changes in screening modalities over time in our model, it would not be possible to determine whether the estimated difference between screening strategies with the initiation age of 50 years versus 40 years was driven by the difference in the initiation age or in the test characteristics between screening modalities. Therefore, it is our view that for modeling studies that compare screening strategies involving different initiation ages and screening intervals, it is preferable to base the model on one screening modality so that findings are more transparent and easier to communicate to policymakers.

This study has several limitations. First, we assumed 100% compliance for each screening schedule, which does not reflect the actual screening pattern at the population level. Nevertheless, because our focus is to compare the relative benefits and costs between different screening strategies, making such comparisons under the scenario of optimal compliance is a reasonable modeling approach. Second, we did not consider the disutility associated with false-positive screening test results, which should have a relatively small impact on QALYs, as shown in CISNET models [57]. This finding is further confirmed in a recent survey study that evaluated the impact of false-positive mammograms on women's anxiety, health utility, and attitudes toward future screening [61]. The authors of the study concluded that although false-positive mammograms were associated with increased short-term anxiety, they were not associated with a measurable health utility decrement. Finally, although the use of ICER allows for a comparison across different strategies, relying on point estimates of ICER to determine the cost-effectiveness of screening strategies is subject to uncertainty because some screening strategies yield very small differences in effectiveness. We thus also used probabilistic analysis to show which strategy has the highest probability of having the largest expected net benefit against different levels of societal willingness to pay. Compared with one-way sensitivity analyses seen in many modeling studies, this approach has the advantage of capturing the combined effect of the uncertainty of all parameters.

Conclusions

Breast cancer inflicts substantial health and financial burden to women in the United States and worldwide. Screening mammography can reduce the disease burden of breast cancer through early detection and timely intervention. Nevertheless, policy makers designing breast cancer screening programs for the population must also consider harms associated with screening mammography, such as false-positive screening results, overdiagnosis and overtreatment. This study applied a microsimulation model to assess the cost-effectiveness of breast cancer screening guidelines updated by professional societies (e.g., USPSTF and ACS) in the US in late 2015/early 2016. Findings from our model suggested that the most cost-effective screening strategy for women at an average risk of developing breast cancer was a hybrid strategy that starts annual mammography screening at the age of age 45 years and switches to biennial screening between the age of 55 years and 75 years – a strategy that conformed to the updated ACS guideline. Future research should extend the model to explore whether the cost-effectiveness of screening strategies would be altered by the rates of screening adherence, especially among selected population subgroups, as well as among women at higher risk of developing breast cancer.

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This study used the linked SEER-Medicare database. Y.-C. T. Shih is a member of the American Cancer Society Cancer Screening Guideline Development Group and had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2018.07.880.

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