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Authors

Yeh, Jennifer M
Lowry, Kathryn P
Schechter, Clyde B
[et al.](#)

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Clinical benefits, harms and cost-effectiveness of breast cancer screening for survivors of childhood cancer treated with chest radiation: A comparative modeling study

Jennifer M. Yeh, PhD¹, Kathryn P. Lowry, MD², Clyde B. Schechter, MD³, Lisa R. Diller, MD⁴, Oguzhan Alagoz, PhD⁵, Gregory T. Armstrong, MD, MSCE⁷, John M. Hampton, MS⁶, Wendy Leisenring, ScD⁸, Qi Liu, MSc⁹, Jeanne S. Mandelblatt, MD, MPH¹⁰, Diana L. Miglioretti, PhD¹¹, Chaya S. Moskowitz, PhD¹², Kevin C. Oeffinger, MD¹³, Amy Trentham-Dietz, PhD⁶, Natasha K. Stout, PhD¹⁴

¹Department of Pediatrics, Harvard Medical School and Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115

²University of Washington, Seattle Cancer Care Alliance, 825 Eastlake Ave. E., Seattle, WA 98109

³Department of Family and Social Medicine, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Block Building 406, Bronx, NY 10461

⁴Dana-Farber/Boston Children's Cancer and Blood Disorders Center, 450 Brookline Avenue, Boston, MA 02115

⁵University of Wisconsin–Madison, 1513 University Avenue, Madison, WI 53706

⁶University of Wisconsin Carbone Cancer Center, 610 Walnut Street, WARF Room 307, Madison, WI 53726

⁷Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, 262 Danny Thomas Pl, Memphis, TN 38105

⁸Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N., Seattle, WA, 98109

⁹University of Alberta, 11405 87th Avenue, Edmonton, Alberta, Canada T6G 1C9

¹⁰Lombardi Comprehensive Cancer Center, Georgetown University, 3300 Whitehaven Street Northwest, Suite 4100, Washington, DC 20007

¹¹Department of Public Health Sciences, University of California Davis School of Medicine, One Shields Avenue, Med-Sci 1C, Room 145, Davis, CA 95616

Corresponding author: Jennifer M. Yeh, PhD, Assistant Professor of Pediatrics, Harvard Medical School, Division of General Pediatrics, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115, Office: 857-218-5577; Fax: 617-730-0957; jennifer.yeh@childrens.harvard.edu.

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¹²Memorial Sloan Kettering Cancer Center, 485 Lexington Ave, 2nd floor, NY, NY 10017

¹³Duke Cancer Institute, 2424 Erwin Dr, Suite 601, Durham, NC 27705

¹⁴Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Landmark Center, 401 Park Drive, Suite 401, Boston, MA 02215

Abstract

Background—Surveillance with annual mammography and breast MRI is recommended for female survivors of childhood cancer treated with chest radiation, yet benefits, harms and costs are uncertain.

Objective—To compare the benefits, harms and cost-effectiveness of breast cancer screening strategies in childhood cancer survivors.

Design—Collaborative simulation modeling using two Cancer Intervention and Surveillance Modeling Network breast cancer models.

Data Sources—Childhood Cancer Survivor Study, published data.

Target Population—Women aged 20+ with a history of chest radiation.

Time Horizon—Lifetime.

Perspective—Payer.

Interventions—Annual MRI +/- mammography, starting at ages 25, 30 or 35.

Outcome Measures—Breast cancer deaths averted, false-positive screens, benign biopsies, incremental cost-effectiveness ratios (ICERs).

Results of Base-Case Analysis—Lifetime breast cancer mortality risk without screening was 10%–11% across models. Compared to no screening, starting at age 25, annual mammography with MRI averted the most deaths (56%–71%), and annual MRI (without mammography) averted 56%–62%. Both had the most screening tests, false-positives, and benign biopsies. For an ICER threshold of <\$100,000 per quality-adjusted life year, starting at age 30 was preferred.

Results of Sensitivity Analysis—Assuming lower screening performance, the benefit of adding mammography to MRI increased in both models, although the conclusions about preferred start age remained unchanged.

Limitations—Elevated breast cancer risk was based on survivors diagnosed with childhood cancer between 1970 and 1986.

Conclusions—Early initiation (at ages 25–30) of annual breast cancer screening with MRI with or without mammography could reduce breast cancer mortality for survivors of childhood cancer by half or more.

INTRODUCTION

Improvements in treatment for childhood cancer over the past five decades have resulted in remarkable survival increases, with more than 80% of children diagnosed today expected to survive five years or longer (1, 2). Despite this success, survivors face very high risks for

treatment-related mortality (3) and late-effects, including secondary breast cancer (4, 5). This includes ~55,000 women in the US who have been treated with 20 Gray (Gy) chest radiation (6). Similar to BRCA1 mutation carriers, an estimated 30% of these survivors will develop breast cancer by age 50 (7). At the same time, overall competing mortality is higher among survivors than women without childhood cancer, reflecting the burden of comorbidities (8, 9), which may reduce health benefits from breast cancer screening and treatment.

Because of this elevated breast cancer risk, earlier initiation and more intensive screening is recommended for these women (10–13). For example, the Children’s Oncology Group (COG) recommends annual mammography screening with adjunct breast magnetic resonance imaging (MRI) starting at age 25 (or 8 years after chest radiation) in survivors of childhood, adolescent or young adult cancer who received 20 Gy chest radiation (14). However, fewer than 50% of at-risk survivors undergo recommended screening (15, 16) and clinicians who care for adult survivors are often unfamiliar with surveillance guidelines (17, 18). Recently, the International Late Effects Of Childhood Cancer Guideline Harmonization Group noted the substantial uncertainty about the balance between the benefits and harms of mammography and MRI in this high-risk population (19).

Decision modeling can facilitate evidence synthesis and provide data to inform guidelines in circumstances when randomized clinical trials are infeasible (20, 21). For example, modeling work by the Cancer Intervention and Surveillance Modeling Network (CISNET) informed the US Preventive Services Task Force (USPSTF) recommendations for breast cancer screening for average-risk women by assessing the benefits and harms for clinically relevant strategies (22, 23). Building upon this work, we used data from the Childhood Cancer Survivor Study (CCSS) (24) and two CISNET breast cancer simulation models to estimate the clinical benefits, harms, and cost-effectiveness of breast cancer screening among childhood cancer survivors previously treated with chest radiation.

METHODS

Overview

To examine breast cancer screening outcomes in survivors of childhood cancer, we used data from the CCSS (25) and adapted two CISNET breast cancer models (26): Model G-E (Georgetown University Medical Center and Albert Einstein College of Medicine) and Model W (University of Wisconsin-Madison) (27, 28) (Appendix Figure 1). The models share common model inputs such as screening test performance and competing mortality risks but vary in their approaches to modeling unobservable breast cancer natural history, including tumor onset and progression (29). Examining results across models thereby provides a range of estimates on breast cancer screening outcomes and helps determine the robustness of the conclusions to structural uncertainty resulting from different approaches to modeling disease natural history. Representative of the larger US population of survivors (25), the CCSS is a multi-institutional cohort study with longitudinal follow-up of North American five-year survivors of common childhood and adolescent cancers diagnosed prior to age 21 between 1970 and 1999 (24). The study was determined not to be human subjects research (Boston Children’s Hospital) or exempt from human subjects review (Georgetown

University Medical Center; University of Wisconsin-Madison) by each Institutional Review Board.

Screening strategies

For a cohort of female survivors of childhood cancer with a history of chest radiation, the models evaluated the following strategies: 1) no screening; 2) digital mammography with MRI screening starting at age 25 (current COG recommendations), 30 or 35 and continuing to age 74, and 3) MRI only starting at age 25, 30 or 35 to age 74. Digital mammography alone was not considered as none of the current guidelines recommend mammography alone as a surveillance strategy in this high-risk population. To estimate efficacy, we assumed 100% adherence to screening and that women will receive the most effective therapy available at the time of breast cancer diagnosis, based on calendar year, age, stage, and estrogen receptor/ human epidermal growth factor 2 status.

Computer Simulation Models

Both Models G-E and W are discrete-event system microsimulation models of US women. Model G-E is a state-transition model that simulates breast cancer natural history without explicitly modeling tumor growth (27). Each breast cancer is assigned a time period in which the cancer can be detected prior to clinical symptoms; screening benefit is a function of detection at younger ages and earlier stage (i.e., stage-shift). Treatment benefits are based on a hazard reduction (i.e., due to lower stage of disease from detection at younger age). Model W simulates breast cancer natural history using a continuous tumor growth model (28). Screening benefit occurs through detection at younger age and smaller tumor size. Treatment benefit is modeled as lifelong “cure” for a proportion of those diagnosed (i.e., no possibility of dying from breast cancer) and no cure for the remainder. In both models, a subset of cancers are nonprogressive (Model G-E) or have limited malignant potential (Model W) (27, 28). Appendix Table 1 provides more detailed model overviews, also available at <https://cisnet.cancer.gov/> and previously described (27, 28, 30). Coding for both models underwent extreme value testing to ensure that results changed in the expected directions. Both models reproduce US temporal trends in incidence and mortality for average-risk women (31) and also have predictive validity by replicating the UK Age Trial results (22, 32).

Model parameters

Breast Cancer Incidence—CCSS participants who were female at time of childhood cancer diagnosis between 1970 and 1986 (median age, 13 years) and treated with 20 Gy of chest radiation (74%) are at a 21.9-fold (95% CI, 19.1 to 25.2) higher risk of developing breast cancer compared to average-risk women based on Surveillance, Epidemiology, and End Results Program (SEER) data (7). These women were diagnosed with Hodgkin lymphoma (55%), Wilms (12%), non-Hodgkin lymphoma (8%) and other tumors. To reflect this elevated risk, we applied age-specific standardized incidence ratios from CCSS participants (relative to age- and calendar year-specific SEER rates) to breast cancer incidence rates in Models G-E and W (Table 1).

Breast Cancer Characteristics—We assumed that the following natural history parameters were similar for breast cancers in childhood cancer survivors as for average-risk women (48): 1) probability and time of disease progression from preclinical to clinical disease, 2) stage distribution among clinically-detected and screen-detected cancers, 3) estrogen receptor/ human epidermal growth factor 2 distribution, and 3) breast cancer-specific mortality rates.

Screening Test Performance—Due to the limited available data on mammography and MRI screening performance specific to childhood cancer survivors, we based estimates of sensitivity and specificity on a meta-analysis which pooled individual-level data from six screening studies on BRCA 1/2 mutation carriers (35), estimated to have cancer risk similar to survivors previously exposed to chest radiation (7). We assumed that past radiation did not affect test performance.

To estimate additional imaging and biopsy rates for combined modality screening, we assumed that 75% of false positive screens were due to MRI (36). Thus, the proportion of women undergoing additional imaging without biopsy (6.7% vs. 6.1%) or having a benign biopsy (14.4% vs. 9.4%) was higher for mammography with MRI versus MRI alone, respectively.

Mortality—Childhood cancer survivors face general population risks of dying but also may develop multiple late complications. We therefore added the excess mortality risks associated with late recurrence of childhood cancer and development of comorbidities (40) to competing causes of mortality (39).

Costs—The costs of screening and diagnostic evaluation of a positive screen were based on US 2018 Medicare reimbursement rates and published estimates (41) (Table 1). For false-positive screen results, we assumed MRI findings led to 30% higher biopsy costs than mammography ones because of higher costs for MRI guidance. For true-positives, we assumed work-up costs were similar for all screening modalities. Cancer treatment costs varied by cancer stage and treatment phase and reflect updated SEER-Medicare costs from a prior analysis (42–44).

Quality of Life—To reflect quality of life among survivors living with late-effects, we used age- and sex-specific utility (quality of life preference) weights for childhood cancer survivors (45). We also incorporated utility deductions for undergoing screening, having false-positive screen results, and undergoing breast cancer treatment (by stage) (46, 47) (Table 1). Due to lack of published estimates for multi-modality screening, we inflated previously published disutility weights for screening mammography (46) by 2-fold for MRI only and 3-fold for mammography with MRI.

Analyses

Both Models GE and W simulated a cohort of 20-year-old female survivors of childhood cancer with a history of chest radiation undergoing breast cancer screening. Model outcomes included lifetime clinical benefits (reduction in breast cancer deaths, gains in life years and quality-adjusted life years), potential harms (number of false-positive screen results, benign

biopsies, overdiagnosed cases), and costs. Overdiagnosed cases were defined as those that would not be clinically detected in the absence of screening.

To illustrate the tradeoffs, we calculated the following harm-benefit ratios: screening tests per death averted, false-positive screens per death averted, benign biopsies per death averted and overdiagnosed cases per death averted. For context, we compared these estimates to published estimates following USPSTF recommendations for biennial mammography for average-risk women aged 50–74 (22, 23). We evaluated the relative performance of strategies, calculating incremental cost-effectiveness ratios (ICERs), defined as the additional cost of a strategy divided by the additional clinical benefit, compared with the next least expensive strategy, and expressed as cost per quality-adjusted life year (QALY) gained. Analyses were conducted from a payer perspective following established recommendations (49, 50).

To reflect uncertainty in key model parameters on results, we conducted sensitivity analyses on the elevated risk of breast cancer associated with chest radiation among survivors, screening performance, and MRI-related costs and disutility weights. Plausible ranges were based on 95% confidence intervals for data used in the base case and expert opinion.

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RESULTS

Clinical benefit and harms of current COG recommendations

Without screening, the lifetime risk of dying from breast cancer among childhood cancer survivors previously treated with chest radiation was 10%–11% across models (Table 2). For all strategies, the estimated benefits were greater in Model W than Model G-E. Compared to no screening, annual mammography and breast MRI starting at age 25 averted the most (56%–71%) breast cancer deaths and increased life years gained by 884–1990 years per 1000 women. Over their lifetimes, 1000 women would have 4188–4878 false-positive screens 1340–1561 benign biopsies. Appendix Table 2 provides estimates of overdiagnosed cases.

Alternative screening strategies: Harm-benefit tradeoffs

In both models, all screening strategies, regardless of start age and screening modality reduced breast cancer deaths by 50% or more (Figure 1). Similarly, adding mammography to MRI or starting screening earlier at age 25 averted more breast cancer deaths, but with greater absolute reductions in Model W than Model G-E, especially when examining start age (Table 2).

For all strategies, the number of false-positive screens per death averted ranged from 31 to 85 per 1000 women and for benign biopsies per death averted, 11 to 27 per 1000 women

across models (Appendix Table 3). These harm-benefit ratios were considerably lower (i.e., more favorable) than benchmarks for average-risk women undergoing USPSTF recommendations for biennial screening (Figure 2). Estimates of overdiagnosed cases per death averted were also lower than average-risk benchmarks (Appendix Table 3).

Cost-effectiveness

When examining COG recommendations, the ICER for annual mammography with MRI starting at age 25 versus no screening was cost-effective at the common threshold of < \$100,000/QALY gained (\$28,890/QALY in Model G-E and \$9,160/QALY in Model W). When considering all screening and start age strategies falling below this threshold, the preferred screening modality was mammography with MRI starting at age 30 (Table 3). ICERs for screening starting at age 25 increased above the threshold relative to starting at age 30, reflecting decreasing marginal gains in QALYs relative to higher incremental costs (Figure 3). For example, in Model W, mammography with MRI screening starting at age 30 (vs. 35) increased QALYs by an additional 215. Starting at age 25 (vs. 30), the gain was only 86 QALYs (Table 2), with even smaller relative increases when discounted to calculate ICERs (Table 3).

Sensitivity analyses

In both models, ICERs for annual screening starting at age 25 became more favorable if the lifetime risk of breast cancer associated with prior chest radiation increased to 64%–67% (vs. 56%–59% in the base case), and less favorable with a lower 43–44% lifetime risk (Appendix Tables 4; Appendix Figure 2). Results were largely unchanged if the elevated risk was 50% lower starting at age 60. If changes in radiotherapy (e.g., decreased volume, dose, field) were assumed to reduce the elevated breast cancer risk by 50% at all ages, ICERs for screening starting at age 25 (compared to no screening) remained below the \$100,000/QALY threshold (\$86,500/QALY in Model G-E and \$38,330/QALY in Model W). When all strategies were considered, the ICER for mammography with MRI starting at age 30 remained below the threshold in Model W but not Model G-E (Appendix Figure 3).

Model W results were more sensitive to changes in test sensitivity and specificity than Model G-E, although overall conclusions about screening strategies and start ages remain unchanged in both models (Appendix Table 4). For example, the 95% lower bound test characteristics for MRI only and MRI with Mammography (35) increased the benefit of adding mammography to MRI in both models, but the ICERs for screening starting at age 30 remained below the \$100,000/QALY threshold (Appendix Figure 4).

Additionally, if the disutilities associated with MRI-related screening and false-positive results were similar to those for mammography and MRI costs were halved, ICERs for screening starting at age 25 (compared to 30) improved in both models, but remained above the \$100,000/QALY threshold in Model G-E. If breast cancer treatment was assumed less effective in survivors (a proxy for possible higher breast cancer-specific mortality among survivors (8)), ICERs for all screening strategies fell as the relative benefits of early detection became greater (Appendix Figure 5).

DISCUSSION

In this collaborative modeling study, we found that in the absence of screening, approximately 1 in 10 female childhood cancer survivors with a history of chest radiation will die from breast cancer compared with 1 in 40 among average-risk women in the general population (23). Screening with mammography and MRI starting at age 25, as currently recommended by the COG, is projected to avert half of expected breast cancer deaths among these high-risk survivors. With this annual schedule, a survivor will have an average of 4 to 5 false-positive screens and 1 to 2 benign biopsies over the course of her lifetime. However, due to the large survival benefits, the harm-benefit tradeoffs for survivors appear to be appropriate, resulting in more favorable harm-benefit ratios than published benchmarks for average-risk women (following USPSTF recommendations). To our knowledge, our study is the first to estimate these harm-benefit ratios for breast cancer screening among survivors of childhood cancer. Further, our findings suggest that starting screening at 30 is cost-effective given commonly cited cost-effectiveness thresholds (51, 52).

Recognizing that screening may be associated with potential anxiety from screening tests and benign biopsies, we evaluated alternative screening strategies which focused on initiating screening at later ages and/or with breast MRI only. We found that all strategies averted more than an estimated 50% of breast cancer deaths among survivors with favorable harm-benefit ratios. However, when both costs and quality of life were considered, ICERs for initiating screening at age 25 (compared to age 30) were considerably higher, reflecting the relatively small incremental benefit (e.g., 2–3 per 1000 women) in breast cancer deaths averted from initiating screening 5 years earlier. We also found that the additional mortality benefit of adding mammography to MRI varied by model, reflecting differences in model assumptions about the impact of detecting smaller or earlier-stage tumors. This is consistent with prior work by the models, with Model G-E generally finding small additional benefits from improvements in screening sensitivity versus more appreciable benefits in Model W. Although not directly comparable given differences in strategies evaluated, our findings are consistent with previous studies which found early initiation of screening among survivors to reduce breast cancer mortality (53) and be cost-effective (54).

Our findings underscore the importance of making sure that young women previously treated with chest radiation are informed about their elevated breast cancer risk and the benefits of routine screening. Both primary care providers and oncologists who care for survivors should discuss breast cancer screening with survivors. Screening guidelines should emphasize the importance of MRI screening (with or without mammography) among survivors. Our findings also highlight the importance of ensuring survivors have access to health insurance coverage for MRI screening. Of note, highlighting the challenges in augmenting rates in these women, the EMPOWER study found only marginal increases in MRI screening rates within 12 months among survivors who received a tailored telephone-delivered motivational interview(16).

Importantly, we did not account for the risk of radiation-induced breast cancer from mammography screening as the additional radiation exposure from mammograms between ages 25 and 39 is small (<0.3%) relative to the total radiation dose in women previously

treated with 20 Gy of chest radiation (6). While the risks of radiation in survivors are likely smaller than for BRCA mutation carriers (who may be more sensitive to radiation-induced DNA damage due to the role of these genes in DNA repair), the use of mammography under the age of 30 remains controversial, and is currently not recommended by the American Cancer Society (11) nor the National Comprehensive Cancer Network (12). Our findings suggest that even without accounting for these additional potential risks, the benefit of adding mammography to MRI screening at these young ages is uncertain, and MRI alone may be a reasonable screening strategy at younger ages.

Additional limitations to our study include using data from survivors diagnosed between 1970 and 1986 to inform the elevated risk of subsequent breast cancer in adulthood now. Our findings suggest that even if the risk declines by half with changes in radiation dose/delivery, initiating screening earlier at younger ages in survivors remains favorable. Second, we based screening test performance on a meta-analysis on BRCA1/2 mutation carriers, who are known to be at higher risk for more aggressive breast cancer subtypes. However, results were stable in sensitivity analyses across a range of test performance (55, 56). We also did not consider digital breast tomosynthesis; its improved specificity (57) may lead to more favorable ICERs. Third, we assumed tumor characteristics and cancer treatment among survivors were similar to average-risk women (6, 48). Treatment options (e.g., use of radiotherapy or cardiotoxic chemotherapy agents) may be more limited for some survivors due to prior treatment exposures, although we found that with lower breast cancer treatment effectiveness, ICERs were even more favorable. Fourth, we assumed that in situ and invasive cancers were equally detectable with mammography or MRI; prior studies have shown that invasive cancers are more likely to be detected by MRI, and ductal carcinoma in situ by mammography. Fifth, we recognize that some childhood cancer survivors are unable to receive MRI and therefore undergo screening mammography only. We did not evaluate this strategy as MRI is recommended by all professional societies for this high-risk cohort and test performance data for mammography screening (without MRI) in high-risk women are limited. Screening costs for young survivors may also be higher than Medicare rates, especially if they are underinsured (58). Additionally, we found considerable uncertainty in estimated overdiagnosed cases between models. However, we note that the biology of overdiagnosis may differ among survivors given prior chest radiation and that estimated cases of overdiagnosis varied little across strategies in both models. Rates of overdiagnosis therefore provide less useful information on the tradeoffs in potential benefits and harms associated with different screening strategies for this unique group of women. Sixth, because of the large number of model parameters and computation time needed, we did not conduct probabilistic sensitivity analyses to evaluate the uncertainty surrounding all input parameters. However, we used two alternative natural history models of breast cancer to understand structural uncertainty and found qualitatively similar results. Lastly, we did not evaluate recently identified genetic markers of susceptibility for secondary breast cancer among survivors (59, 60). Survivors without a history of chest radiation have also been shown to be at elevated risk for breast cancer (56, 61, 62). Future planned analyses include using modeling to understand how this information can refine and inform screening guidelines for at-risk survivors.

In conclusion, female childhood cancer survivors previously treated with chest radiation are at high risk from dying from breast cancer and this early mortality can be averted with initiation of annual breast cancer screening. Our models suggest that annual screening with MRI (with or without mammography) starting at ages 25–30 can avert half or more of the expected deaths, with an acceptable rate of false-positive screens. Our findings highlight the importance of MRI in reducing deaths from breast cancer among young women previously exposed to chest radiation. Identifying effective policies and interventions to reduce barriers to screening should be priorities for policymakers to ensure comprehensive and coordinated care for these high-risk survivors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Reproducible Research Statement

Study protocol

Available from Dr. Yeh (email, jennifer.yeh@childrens.harvard.edu).

Computer code

Detailed information about the models is available online at <https://cisnet.cancer.gov/breast/profiles.html> and available in references (27) and (28).

Analytic dataset

Output data from models available from Dr. Yeh (email, jennifer.yeh@childrens.harvard.edu).

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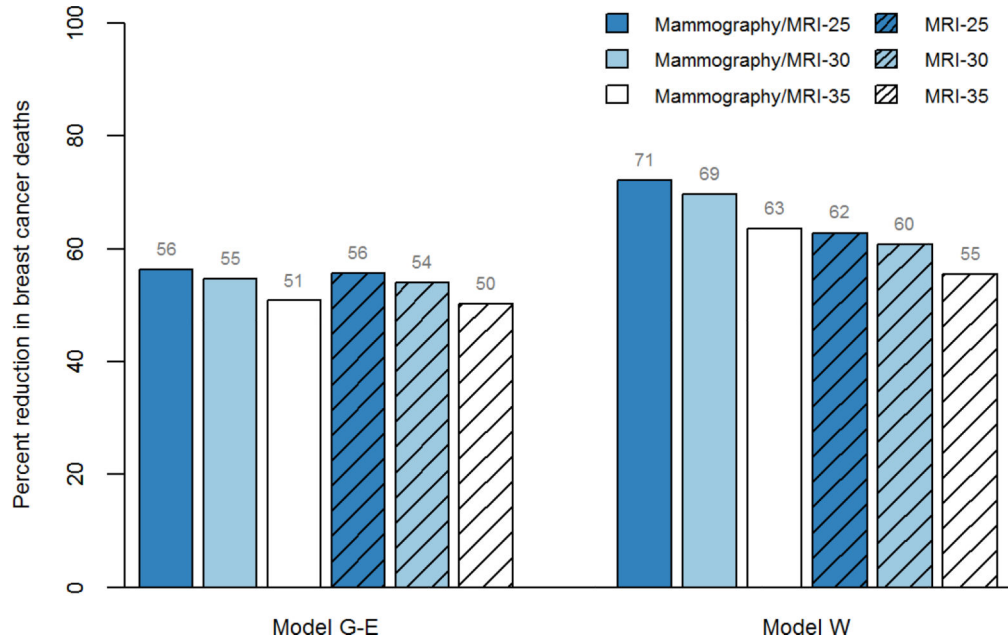


Figure 1. Reduction in Breast Cancer Mortality for Screening Strategies Varying by Modality and Start Age among Childhood Cancer Survivors.

Shown are estimates for the reduction in breast cancer deaths for each screening strategy varying by modality (mammography with MRI, MRI only) and start age (25, 30 and 35) compared to no screening. G-E, Georgetown-Einstein; MRI, magnetic resonance imaging; W, Wisconsin.

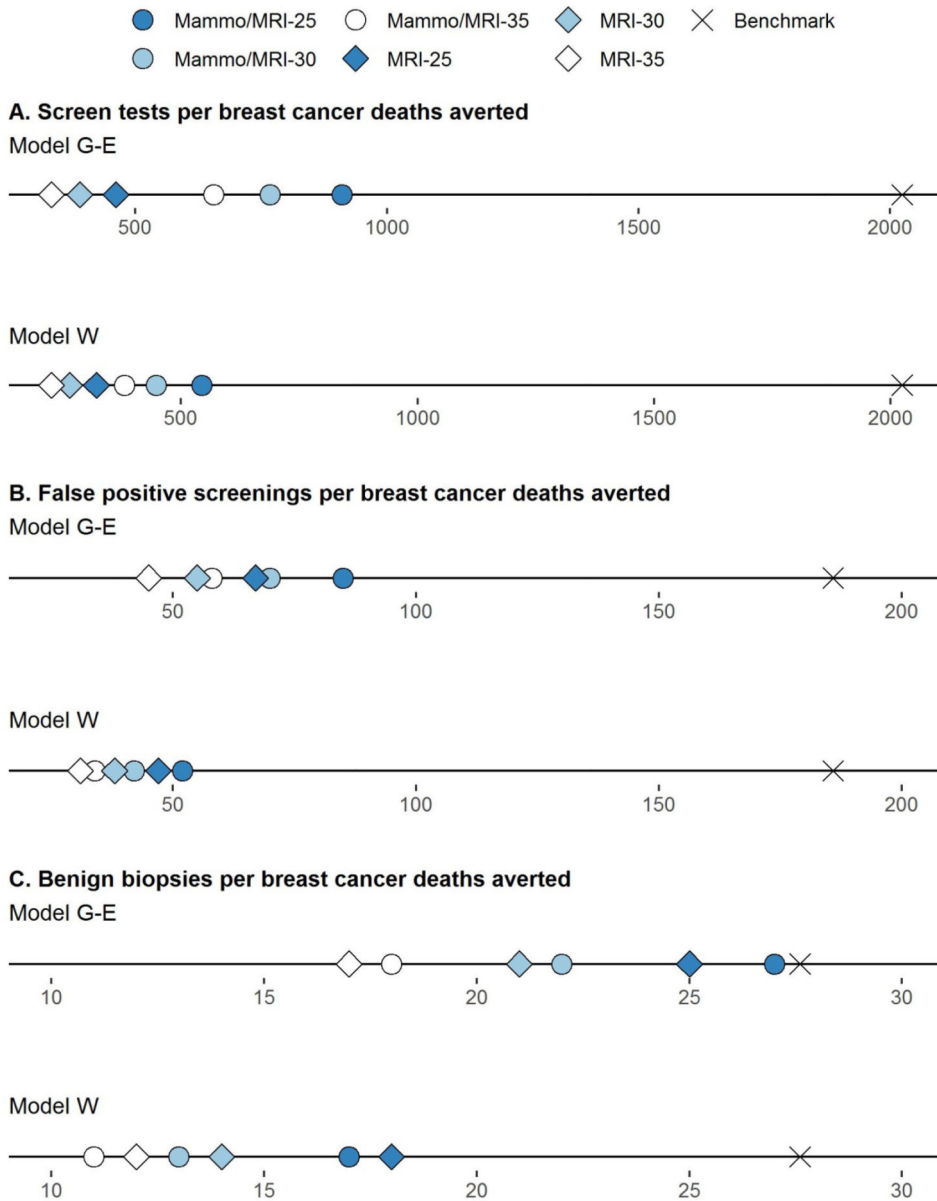


Figure 2. Harm-Benefit Ratios for Screening Strategies Varying by Modality and Start Age among Childhood Cancer. Shown are estimates for number of screening tests per breast cancer death averted (Panel A), false positive screens per breast cancer death averted (Panel B) and benign biopsies per breast cancer death averted (Panel C) for each screening strategy. For context, benchmark published estimates for harm-benefit ratio are shown for average-risk women in the general population undergoing USPSTF screening recommendations (biennial mammography between ages 50 and 74) (22, 23) Estimates for all screening strategies in both Model W and G-E were more favorable than benchmark ratios for average-risk women. G-E, Georgetown-Einstein; mammo, mammography; MRI, magnetic resonance imaging; W, Wisconsin.

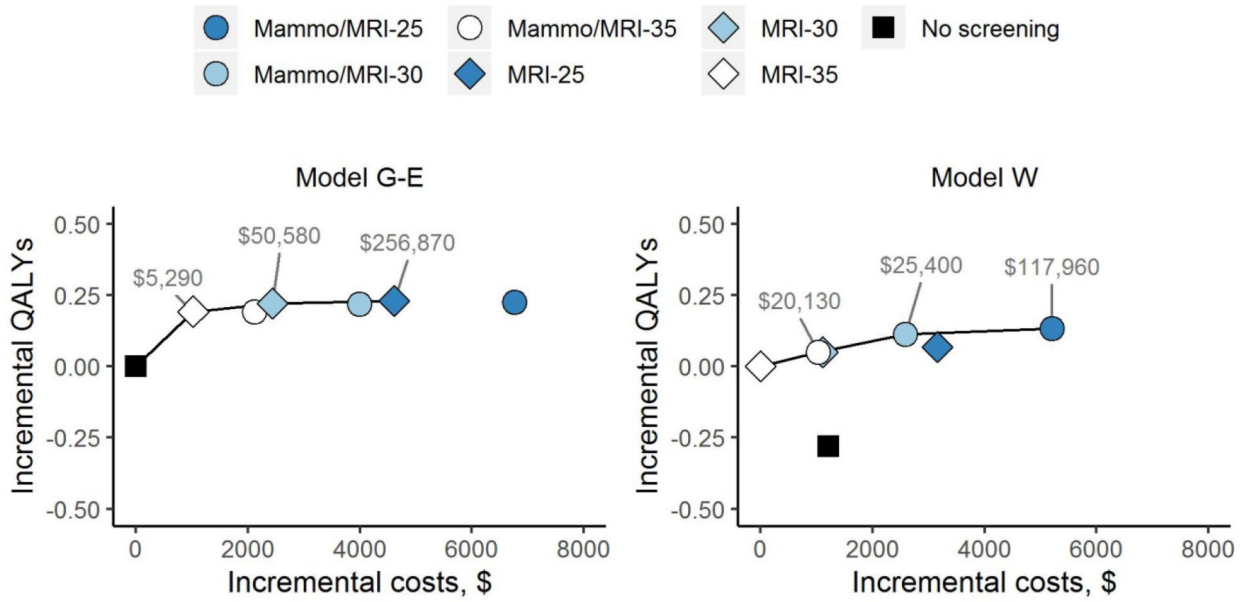


Figure 3. Cost-Effectiveness Efficiency Frontier for Screening Strategies Varying by Modality and Start Age.

Shown are incremental discounted costs per gain in discounted QALYs for each screening strategy compared to the baseline strategy in Model W (Panel A) and Model G-E (Panel B). Because of the greater estimated reduction in breast cancer deaths in Model W vs. Model GE, no screening was dominated (and eliminated) by MRI-35 and the baseline comparator was MRI-35 in Model W and no screening in Model G-E. Strategies on the efficiency frontier (solid line) have incremental cost-effectiveness ratios (ICERs), expressed as cost per QALY gained, as shown and offer both higher effectiveness and lower cost than those strategies below it. Both costs and benefits were discounted 3% annually. G-E, Georgetown-Einstein; mammo, mammography; MRI, magnetic resonance imaging; QALY, quality-adjusted life year; W, Wisconsin.

Table 1.

Model Input Parameters

Parameter	Description	Data Source
Natural history of breast cancer		
Incidence in the absence of screening	Age-period-cohort model calibrated to observed SEER program rates. Adjusted to reflect the elevated risk among childhood cancer survivors with a history of chest radiation using age-specific standardized incidence ratios (SIR): 40.2 (95% CI, 25.3, 63.7) for 20–29 years old, 30.6 (95% CI, 25.1, 37.2) for 30–39 year old, 16.6 (95% CI, 13.2–20.7) for 40–49 years old, and 15.3 (95% CI, 8.2, 28.4) for 50 years old.	(7, 33)
Stage distribution *	Stage distribution among women with clinically-, interval- and screen-detected cancer by age group (<50, 50–64, 65). Based on data for digital mammography.	BCSC
ER/HER2 joint distribution	Probability of ER/HER2 status conditional on age and stage/tumor size at diagnosis	BCSC
Sojourn time	Sojourn time, defined as the period of time preclinical disease is detectable by screening but asymptomatic, by joint ER/HER2 status and age. Assumed tumor characteristics in survivors similar to those in average-risk women.	(34)
Mean stage dwell time/tumor progress rates	Dwell time, defined as the time spent within a stage, varies by age and ER/HER2 status, and by model. Assumed tumor characteristics in survivors similar to those in average-risk women.	(27–29)
Breast cancer screening		
Sensitivity/detection rates	Sensitivity by age group for digital mammography with MRI (<50 years: 0.932 [95% CI, 0.793, 0.980]; 50 years: 0.941 [95% CI, 0.777, 0.987] and MRI (without mammography) (<50 years: 0.857 [95% CI, 0.694, 0.941]; 50 years: 0.844 [95% CI, 0.618–0.948].	(35)
Specificity	Specificity by age group for mammography with MRI (<50 years: 0.787 [95% CI, 0.706, 0.850]; 50 years: 0.853 [95% CI, 0.785, 0.902] and MRI (<50 years: 0.835 [95% CI, 0.776, 0.881]; 50 years: 0.885 [95% CI, 0.835, 0.922]. Assuming 75% of false positive screens were due to MRI, the proportion of women undergoing additional imaging without biopsy (6.7% vs. 6.1%) or having a benign biopsy (14.4% vs. 9.4%) was higher for mammography with MRI versus MRI only.	(22, 23, 35, 36) BCSC
Breast cancer treatment		
Treatment use	Assume receipt of and adherence to the most effective available treatment specific to age, stage and ER/HER2 status. Optimal therapy assumed similar efficacy for surgery (lumpectomy or mastectomy) with or without radiation.	(37)
Treatment effects	Meta-analysis of clinical trial results. Modeled as a reduction in breast cancer-specific mortality risk or increase in proportion cured in the absence of adjuvant treatment.	(38)
Survival		
Breast cancer survival	Long-term breast cancer survival before adjuvant treatment by joint ER/HER2 status, age group, and stage or tumor size.	(34)
Non-breast cancer mortality	Age- and cohort-specific all-cause mortality rates by year, modified to include survivor-specific late mortality risks based on female CCSS participants diagnosed between 1970 and 1999 treated with chemotherapy and radiation.	(39, 40)
Costs, US 2018 dollars		
Screening mammography	\$141	CMS
Screening MRI	\$550	CMS
Work-up after false-positive screen result	Imaging costs: \$157 (all ages). Biopsy costs by age for mammography: \$1040 for ages 20–49, \$1508 for ages 50–64, \$1516 for ages 65–74, and \$1606 for ages 75+. Assumed biopsy costs for MRI were 30% higher than for mammography.	(41)
Work-up after true-positive screen result	By age: \$2556 for ages 20–49, \$2400 for ages 50–64, \$2412 for ages 65–74, and \$2034 for ages 75+.	(41)

Parameter	Description	Data Source
Breast cancer treatment	By stage during initial treatment: \$14,440 for DCIS, \$23,573 for local stage, \$40,215 for regional stage, and \$54,446 for distant stage. During the last year of life among women with cancer that was not cured/progressed, depending on stage at diagnosis: \$55,428 for DCIS, \$57,912 for local stage, \$62,741 for regional stage, and \$79,411 for distant stage.	(42–44)
Utilities		
Survivors	Age- and sex-specific quality-of-life utilities among survivors of childhood cancer.	(45)
Screening mammography	Utility weight of 0.994 for 1 week.	(46)
Screening MRI	Assumed disutility for MRI, including potential side effects from gadolinium, was 2-fold higher than mammography, for utility weight of 0.988.	(46)
Diagnostics after positive screen	Utility weight of 0.895 for 5 weeks for mammography. Assuming disutility is proportional to biopsy rate, utility weight of 0.79 for 5 weeks for MRI and 0.815 for mammography with MRI for 5 weeks.	(46)
Cancer treatment	By stage: Utility weight of 0.9 or 2 years for DCIS and local stage, 0.75 for 2 years for regional stage, and 0.6 until death for distant stage.	(47)

Abbreviations: BCSC, Breast Cancer Surveillance Consortium; CCSS, Childhood Cancer Survivor Study; CMS, Centers for Medicaid and Medicare Services; DCIS, ductal carcinoma in situ; ER, estrogen receptor; HER2, human epidermal growth factor 2; MRI, magnetic resonance imaging.

* Stage based on Surveillance, Epidemiology, and End Results (SEER) historical staging for Model W and American Joint Committee on Cancer (version 6) for Model G-E.

Table 2. Lifetime Benefits and Harms of Screening Strategies Varying by Modality and Start Age

Strategy*	Breast cancer deaths per 1000 women, n		Reduction in breast cancer deaths, %†		Life years gained per 1000 women, LYs‡		QALYs gained per 1000 women, QALYs‡		Screening tests per 1000 women, n‡		False-positive screens per 1000 women, n‡		Benign biopsies per 1000 women, n‡	
	Model G-E	Model W	Model G-E	Model W	Model G-E	Model W	Model G-E	Model W	Model G-E	Model W	Model G-E	Model W	Model G-E	Model W
No screening	101.5	112.1	--	--	--	--	--	--	--	--	--	--	--	--
MRI-35	50.6	50.7	50.2	54.8	1109	1774	475	851	16,928	13,901	2289	1909	870	726
Mammo/MRI-35	49.9	41.8	50.8	62.7	1122	2095	479	1079	33,798	26,750	2969	2418	950	774
MRI-30	46.7	44.9	54.0	60.0	1242	2034	564	1030	21,351	17,840	3002	2550	1141	969
Mammo/MRI-30	46.0	35.0	54.7	68.8	1255	2408	566	1294	42,644	34,566	3892	3244	1245	1038
MRI-25	45.0	42.6	55.7	62.0	1304	2148	599	1101	26,053	22,310	3764	3283	1430	1248
Mammo/MRI-25	44.4	32.3	56.3	71.2	1317	2544	599	1380	52,048	43,466	4879	4188	1561	1340

G-E, Georgetown-Einstein; LYs, life years; mammo, mammography; MRI, magnetic resonance imaging; QALYs, quality-adjusted life years; W, Wisconsin.

* Strategies rank ordered by increasing reduction in breast cancer deaths in Model G-E

† Compared to no screening.

‡ Life years per 1000 women for no screening was 4347 in Model W and 4523 in Model G-E.

∥ Quality-adjusted life years per 1000 women for no screening was 3195 in Model W and 3318 in Model G-E.

Table 3. Cost-Effectiveness of Breast Cancer Screening for Strategies Varying by Modality and Start Age: Cost per QALY

Strategy*	Model G-E			Model W		
	Discounted costs per 1000 women, \$ [†]	Discounted QALYs per 1000 women, QALYs [†]	ICER, \$ per QALY [†]	Discounted costs per 1000 women, \$ [†]	Discounted QALYs per 1000 women, QALYs [†]	ICER, \$ per QALY [†]
No screening	\$13,495,990	17378.0	Baseline comparator	\$11,923,450	17089.9	‡
MRI-35	\$14,516,990	17571.4	\$5,290	\$10,716,760	17369.9	Baseline comparator
Mammo/MRI-35	\$15,615,310	17571.1	\$11,000 //	\$11,745,380	17421	\$20,130
MRI-30	\$15,928,260	17599.3	\$50,580	\$11,822,100	17420.6	\$21,800 [§]
Mammo/MRI-30	\$17,494,210	17597.7	\$113,200 [¶]	\$13,302,130	17482.3	\$25,400
MRI-25	\$18,111,660	17607.8	\$256,870	\$13,871,490	17438.7	\$120,120 ^{**}
Mammo/MRI-25	\$20,256,890	17604.6	\$816,720 ^{††}	\$15,920,920	17504.5	\$117,960

G-E, Georgetown-Einstein; ICER, incremental cost-effectiveness ratio; mammo, mammography; MRI, magnetic resonance imaging; QALYs, quality-adjusted life years; W, Wisconsin.

* Strategies rank ordered by increasing reduction in breast cancer deaths in Model G-E

[†] Costs and benefits discounted 3% annually.

[‡] Strategy was dominated by Mammo/MRI-35, MRI-35 and Mammo/MRI-30 (i.e. more costly and less effective).

// Strategy was dominated by Mammo/MRI-35, however because the difference in discounted costs and QALYs between the two strategies are close, the ICER where the reference case is No screening is reported.

[§] Strategy was dominated by Mammo/MRI-35, however because the difference in discounted costs and QALYs between the two strategies are close, the ICER where the reference case is MRI-35 is reported.

[¶] Strategy was dominated by MRI-30, however because the differences in discounted costs and QALYs between the two strategies are close, the ICER where the reference case is MRI-35 is reported.

** Strategy was dominated by Mammo/MRI-30, however because the difference in discounted costs and QALYs between the two strategies are close, the ICER where the reference case is Mammo/MRI-35 is reported.

^{††} Strategy was dominated by MRI-25, however because the differences in discounted costs and QALYs between the two strategies are close, the ICER where the reference case is MRI-30 is reported.