Tailoring Breast Cancer Screening Intervals by Breast Density and Risk for Women Aged 50 Years or Older: Collaborative Modeling of Screening Outcomes.

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ABSTRACT

Background

Biennial screening is generally recommended for average-risk women aged 50 to 74 years, but tailored screening may provide greater benefits.

Objective

To estimate outcomes for various screening intervals after age 50 based on breast density and risk for breast cancer.

Design

Collaborative simulation modeling using national incidence, breast density, and screening performance data.

Setting

United States

Patients

Women aged 50 years or older with various combinations of breast density and relative risk (RR) of 1.0, 1.3, 2.0, or 4.0.

Interventions

Annual, biennial, or triennial digital mammography screening from ages 50 to 74 years (vs. no screening) and ages 65 to 74 years (vs. biennial digital mammography from ages 50 to 64 years)

Measurements

Lifetime breast cancer deaths, life expectancy and quality-adjusted life-years (QALYs), false-positive mammograms, benign biopsy results, overdiagnosis, cost-effectiveness, and ratio of false-positive results to breast cancer deaths averted

Results

Screening benefits and overdiagnosis increase with breast density and RR. False-positive mammograms and benign results on biopsy decrease with increasing risk. Among women with fatty breasts or scattered fibroglandular density and an RR of 1.0 or 1.3, breast cancer deaths averted were similar for triennial versus biennial screening for both age groups (50 to 74 years, median of 3.4 to 5.1 vs. 4.1 to 6.5 deaths averted; 65 to 74 years, median of 1.5 to 2.1 vs. 1.8 to 2.6 deaths averted). Breast cancer deaths averted increased with annual versus biennial screening for women aged 50 to 74 years at all

levels of breast density and an RR of 4.0, and those aged 65 to 74 years with heterogeneously or extremely dense breasts and an RR of 4.0. However, harms were almost 2-fold higher. Triennial screening for the average-risk subgroup and annual screening for the highest-risk subgroup cost less than $100 000 per QALY gained

Limitations

Models did not consider women younger than 50 years, those with an RR less than 1, or other imaging methods.

Conclusions

Average-risk women with low breast density undergoing triennial screening and higher-risk women with high breast density receiving annual screening will maintain a similar or better balance of benefits and harms than average-risk women receiving biennial screening.

Primary Funding Source

National Cancer Institute

INTRODUCTION

Debate surrounding breast cancer screening for women in their 40s continues; however, there is a greater consensus about U.S. guidelines for average-risk women 50 or older (1, 2), with groups now recommending biennial mammography from ages 50 or 55 to 74 years (3, 4). Biennial screening is supported by clinical trials (5, 6), observational studies (5, 7), and modeling results (8). Present recommendations also acknowledge that implementing screening in clinical practice should involve shared decision making to consider preferences, risk levels, and breast density (3, 4). However, data to guide clinicians and women in making personalized decisions about screening intervals based on such factors are limited.

Observational data (7, 9) and modeling studies (10, 11) suggest that annual screening may be more effective than biennial screening for women at high risk for breast cancer due to dense breasts and other risk factors, further, triennial screening may retain most of the benefit of biennial screening but may be less harmful and more cost-effective for low-risk women with low density. However, past empirical research on alternative screening intervals did not include mortality outcomes (12). Moreover, most prior modeling studies have relied on single models (10, 11), data on film-screen mammography and older treatment regimens (10, 11, 13), and did not consider changes in breast density as women age (10), or triennial intervals (8).

To fill this gap, the Cancer Intervention and Surveillance Modeling Network (14) collaborating with the Breast Cancer Surveillance Consortium (BCSC) (a longstanding network of 6 U.S. breast imaging registries with links to tumor and pathology registries (15)), used 3 well-established models to evaluate various screening intervals for digital mammography among subgroups of women based on age, risk, and breast density. Outcomes were projected for women aged 50 (or 65) years who were deciding whether to initiate (or continue) biennial screening until age 74 years or to have annual or triennial screening. Study results are intended to inform discussions about implementing tailored breast cancer screening intervals to maximize screening benefits while minimizing harms.

METHODS

Overview of Breast Cancer Screening Strategies

The study included the following 3 microsimulation models: Model E (Erasmus Medical Center, Rotterdam, Netherlands), Model GE (Georgetown University Medical Center, Washington, DC; and Albert Einstein College of Medicine, Bronx, New York), and Model W (University of Wisconsin–Madison, Madison, Wisconsin; and Harvard Medical School,

Boston, Massachusetts). These models were either exempt from human subjects review or approved by review boards at each institution.

The models used a lifetime horizon to evaluate screening strategies for 2 populations, women aged 50 years who were starting screening for the first time and those aged 65 years who had received biennial screening from ages 50 to 64 years. We selected these populations because there is a consensus on screening women in their 50s and because at age 65 years, increases in competing mortality risks and decreases in breast density might alter the balance of benefits and harms.

Strategies for each age group varied by screening interval (annual, biennial, and triennial) and were compared with no screening. These intervals were applied to population subgroups based on combinations of the following 4 breast density levels, as defined by the American College of Radiology's Breast Imaging Reporting and Data System: almost entirely fat ("a"), scattered fibroglandular density ("b"), heterogeneously dense ("c"), or extremely dense ("d") (16)], and 4 exemplar relative risk (RR) levels, which incorporated risk factors other than breast density. These levels represent common risk factors considered alone or in combination: 1.0 (average), 1.3 (for example, postmenopausal obesity) (17-27), 2.0 (for example, history of benign breast biopsy results), and 4.0 (history of lobular carcinoma in situ) (25-29) (**Appendix Table 1**). Populations with risk suggestive of mutations in breast cancer susceptibility genes 1 and 2 were not included in these analyses.

Model Overview

The models shared common inputs but used different structures and underlying assumptions (**Appendix Table 2**) (8, 14). They started with estimates of age-specific breast cancer incidence (31) and survival trends specific to breast cancer stage, estrogen receptor (ER) status, and human epidermal growth factor receptor 2 (HER2) status (30) all without screening or adjuvant treatment. Incidence in the absence of screening was calibrated from an age–period–cohort model that accounted for changes in underlying risk (for example, secular patterns in postmenopausal hormone use) (31). Tumors had a range of preclinical periods during which they could be detected by screening (that is, sojourn times). Data on screening and ER/HER2-specific adjuvant treatment were added to generate breast cancer–specific incidence and mortality (14). Models have been validated using data from the U.K. Age trial During the preclinical detectable period, screening could result in the identification and treatment of earlier-stage or smaller tumors and lead to a reduction in breast cancer mortality reduction (**Appendix Figure 1**). All models assumed that a portion of ductal carcinoma in situ lesions was non-progressive and nonlethal; model W also considered that some types of small invasive cancer would not progress.

Model Input Parameters

The models used a common set of age-specific variables for population demographics (32), breast cancer natural history and risk (30, 31, 33-36), digital mammography (37, 38), breast density, treatment (39-41), mortality (30), costs (42, 43), and quality of life (**Table 1 and Appendix Table 2)** (14, 44-46). Each model also included parameters to represent preclinical detectable times, lead time, and age- and ER/HER2-specific stage distribution in screen- versus non–screendetected cancer based on each model's specific structure. These model-specific parameters were based on assumptions about combinations of values that reproduced U.S. trends in breast cancer incidence and breast cancer–specific mortality from 1975 to 2010 in the SEER (Surveillance, Epidemiology, and End Results) program (47). To isolate the effect of various screening strategies, all models assumed 100% adherence to screening and receipt of the most effective treatment. The population included women born in 1970 and followed until death. This birth cohort was chosen because these women experience modern conditions (for example, digital mammography performance, treatment effectiveness, and competing mortality) and for consistency with recent collaborative modeling reports (8). In each simulation, subgroups of women were followed from age 25 years until death or age 100 years. Subgroups were defined on the basis of combinations of 4 RR levels (1.0, 1.3, 2.0, and 4.0) and 4 breast density levels, with the combination of breast density levels and other factors treated multiplicatively. The risk level modified the underlying breast cancer incidence in the absence of screening. We assumed that risk level was constant over age and did not affect other model parameters. Women were assigned to either the same breast density category or the next lower category at ages 50 and 65 years based on observed age-specific prevalence in the BCSC(27, 48). Density also affected mammography performance (**Table 1 and Appendix Table 3**).

Digital mammography sensitivity and specificity were based on age, initial or subsequent screening, screening interval, and breast density using BCSC data (Table 1 and Appendix Table 3). Models GE and W used these data for calibration, and model E fit estimates from the BCSC and other sources Specificity data were used to estimate rates of false-positive mammograms. The BCSC rates of biopsy recommendations were applied to these estimates to calculate the number of benign biopsy results. Treatment effectiveness was based on clinical trials and modeled as a reduction in mortality risk (model GE) or an increase in the proportion cured (models E and W) compared with age-, stage-, and ER/HER2- specific survival in the absence of therapy (39). Women died of either breast cancer or other causes.

Screening Outcomes

Primary outcomes were lifetime benefits and harms; secondary outcomes were use of services and costs. Benefits included breast cancer deaths averted and life-years and

Table 1 Model Input Parameters

Parameter	Description	Data Source
Population Demographics		
Birth cohorts	1970 birth cohort	(32)
Natural History of Breast Cancer		
Incidence in the absence of screening	An age-period-cohort model is used as a starting point for calibration to observed SEER Program rates.	(31)
Stage distribution	Stage distribution among clinically-detected and digital screen-detected women by age group (<50, 50–64, ≥65 years), screening round (first, subsequent), and screening interval (annual, biennial, triennial).	BCSC data from 1994–2013 (digital from 2003–2013)
ER/HER2 joint distribution	Probability of ER/HER2 conditional on age and stage at diagnosis.	BCSC
Sojourn time	Sojourn time by joint ER/HER2 status and age.	(30)
Mean stage dwell time/tumor growth rates	Varies by models; can vary by age and/or ER/HER2 status.	(33-35)
Breast Cancer Screening		
Mammography use	Assume all women are screened by digital mammography.	(37, 38)
Sensitivity/ detection rates of digital screening	Sensitivity of initial and subsequent digital mammography by age group, screening interval (annual, biennial, triennial), and breast density. See Appendix Table 3.	BCSC
Specificity	False-positive mammograms are calculated as the difference between the overall number of positive mammograms in a screening scenario minus the number of positive mammograms among breast cancer cases.	BCSC
Prevalence of breast density	Prevalence of breast density (BI-RADS a, b, c, d) by age group. Density is assigned at age 40 years and can decrease by one level or remain the same at age 50 years and again at age 65 years.	BCSC
Risk levels for density	Risk of breast cancer based on BI-RADS relative to average density by age group.	BCSC
Risk levels for factors other than density	RR=1 is used at the referent for average population. RR=1.3, 2.0, and 4.0 are used as levels associated with common risk factors.	(36)
Breast Cancer Treatment		
Treatment use	Assume receipt of and adherence to the most effective available treatment specific to age, stage and ER/HER2 status.	1997–2010 (40, 41)
Treatment effects	Meta-analyses of clinical trial results.	(39)
Survival		
Breast cancer survival	26-year breast cancer survival before adjuvant treatment by joint ER/HER2 status, age group, and AJCC/SEER stage or tumor size	(30)
Non-breast cancer mortality	Age- and cohort-specific all-cause mortality rates by year.	Vanness D, Personal communication, 2015
Costs		
Screening mammogram	$138.28	Medicare reimbursement
Work-up after false-positive mammogram	Imaging costs: $141.42 (all ages). Biopsy costs by age: $1,354.05 for ages 50-64; $1,361.39 for ages 65-74; and $1,442.19 for ages 75-100. Biopsies applied to 10.6% of women screened within each age group.	(42)

Table 1 Model Input Parameters (continued)

Parameter	Description	Data Source
Work-up after true positive mammogram	By age: $2,154.58 for ages 50-64; $2,166.52 for ages 65-74; and $1,826.80 for ages 75-100.	(42)
Breast cancer treatment	By stage during initial treatment: $13,695.67 for DCIS and local stage; $25,893.77 for regional stage; and $39,990.86 for distant stage. During the last year of life among women with cancers that were not cured/progressed, depending on stage at diagnosis: $37,070.10 for DCIS and local stage; $43,878.64 for regional stage; and $61,544.91 for distant stage.	(43)
Utilities		
Healthy women	Age-specific quality of life utilities among women without breast cancer.	(45)
Screening mammogram	0.994 for 1 week	(44)
Diagnostics after positive mammogram	0.895 for 5 weeks	(44)
Cancer treatment	By stage: 0.9 for 2 years for DCIS and local stage; 0.75 for 2 years for regional stage; and 0.6 until death for distant stage.	(46)

Abbreviations: AJCC, American Joint Committee on Cancer; BCSC, Breast Cancer Surveillance Consortium; BI-RADS, Breast Imaging Reporting and Data System; DCIS, ductal carcinoma in situ; ER, estrogen receptor; HER2, human epidermal growth factor 2; RR, relative risk; SEER, Surveillance, Epidemiology, and End Results.
Note: Not all models use all parameters; some models use parameters as direct inputs and others use them as a target for calibration or other estimation (See Appendix Table 2).

quality-adjusted life-years (QALYs) gained. The QALYs were based on utilities for the general U.S. population estimated both with and without adjustments for having a screening examination (0.006 for 1 week per examination = –1 hour per examination) and having a positive screening result and undergoing diagnostic evaluation (0.0105 for 5 weeks = –8.8 hours). We also adjusted for breast cancer treatment (Table 1).

Harms included false-positive mammograms, benign biopsies, and overdiagnosis. The rate of false-positive mammograms was the number read as abnormal in women without cancer divided by the total. Benign biopsies were defined as a biopsy recommendation among women with false-positive screening results (49). Overdiagnosis was defined as screen-detected cancer that would not have been diagnosed in a woman's lifetime in the absence of mammography (14, 50).

Costs (reported in 2014 U.S. dollars) were estimated based on the number of mammograms; evaluation of positive mammograms, including additional imaging or biopsy among women with cancer and those with false-positive mammograms; and stage-specific cancer treatments based on Medicare reimbursement schedules and published studies (Table 1).

Table 2 Lifetime benefits of screening annually, biennially or triennially per 1000 women screened by relative risk, breast density, and age group across 3 models.

		Breast cancer deaths averted vs. no screening, median (range across models)			Life years gained vs. no screening, median (range across models) *		
Density	**RR**	**Triennial**	**Biennial**	**Annual**	**Triennial**	**Biennial**	**Annual**
Ages 50-74†							
Almost entirely fatty	1	3.4 (1.8-3.6)	4.1 (2.4-4.3)	4.7 (3.2-5.6)	50 (35-64)	64 (47-73)	84 (62-85)
	1.3	4.4 (2.4-4.6)	5.3 (3.1-5.5)	6.0 (4.1-7.1)	64 (46-82)	82 (60-94)	108 (80-109)
	2	6.4 (3.6-7.0)	8.0 (4.8-8.0)	9.1 (6.2-10.3)	94 (69-124)	120 (92-142)	159 (122-163)
	4	11.0 (7.2-13.1)	13.8 (9.2-15.0)	17.2 (12.0-17.7)	164 (136-235)	209 (177-269)	277 (233-309)
Scattered fibroglandular	1	4.0 (2.9-5.9)	5.2 (3.8-6.8)	6.9 (5.1-7.9)	59 (56-107)	77 (74-123)	106 (101-143)
	1.3	5.1 (3.7-7.5)	6.5 (4.9-8.7)	8.7 (6.6-10.1)	75 (72-137)	97 (95-158)	134 (129-184)
	2	7.2 (5.6-11.2)	9.2 (7.4-12.9)	12.3 (9.9-15.0)	109 (107-204)	144 (139-236)	194 (191-275)
	4	11.5 (10.8-20.2)	14.7 (13.9-23.3)	19.4 (18.4-27.0)	207 (175-372)	269 (227-430)	360 (308-502)
Heterogeneously dense	1	4.8 (3.3-8.4)	6.3 (4.4-9.8)	8.4 (6.1-11.7)	72 (64-149)	94 (86-175)	130 (122-210)
	1.3	6.0 (4.2-10.7)	7.7 (5.6-12.4)	10.4 (7.8-14.8)	90 (82-190)	117 (110-223)	161 (155-267)
	2	8.3 (6.3-15.5)	10.6 (8.3-18.1)	14.3 (11.6-21.6)	124 (122-278)	162 (162-326)	230 (224-392)
	4	12.4 (11.4-26.5)	15.8 (15.1-31.0)	21.0 (20.8-37.1)	221 (192-485)	294 (248-568)	411 (338-685)
Extremely dense	1	5.1 (3.1-9.9)	6.5 (4.2-11.7)	8.9 (6.0-14.4)	75 (61-174)	98 (82-206)	138 (121-255)
	1.3	6.2 (4.0-12.5)	8.0 (5.4-14.7)	10.9 (7.7-18.1)	93 (79-219)	122 (106-261)	170 (155-323)
	2	8.4 (5.9-17.9)	10.8 (7.9-21.1)	14.7 (11.4-26.0)	127 (115-317)	166 (155-376)	231 (226-468)
	4	12.0 (10.4-29.3)	15.4 (14.0-34.7)	20.5 (20.2-42.9)	204 (187-534)	277 (242-634)	402 (332-789)
Ages 65-74‡							
Almost entirely fatty	1	1.5 (0.8-1.6)	1.8 (1.0-2.0)	2.3 (1.4-2.4)	16 (11-21)	19 (15-26)	26 (21-31)
	1.3	1.9 (1.0-2.0)	2.3 (1.4-2.6)	3.0 (1.9-3.1)	20 (14-27)	24 (19-34)	34 (27-40)
	2	2.7 (1.5-3.0)	3.2 (2.1-3.9)	4.3 (2.8-4.4)	28 (20-40)	33 (29-50)	47 (41-59)
	4	4.2 (2.6-5.4)	5.1 (3.8-7.0)	6.8 (5.0-8.0)	44 (37-71)	54 (52-92)	73 (73-107)
Scattered fibroglandular	1	1.7 (1.1-2.3)	2.1 (1.6-2.9)	3.0 (2.2-3.4)	18 (17-30)	23 (22-39)	33 (32-45)
	1.3	2.1 (1.5-2.9)	2.6 (2.1-3.7)	3.6 (2.9-4.3)	22 (21-38)	30 (27-49)	42 (39-58)
	2	2.9 (2.1-4.2)	3.5 (3.0-5.4)	4.9 (4.1-6.3)	30 (29-55)	43 (36-71)	60 (53-84)
	4	4.0 (3.6-7.2)	5.3 (4.9-9.4)	7.2 (6.8-10.9)	50 (41-96)	74 (50-124)	102 (73-146)
Heterogeneously dense	1	2.0 (1.2-3.6)	2.5 (1.8-4.7)	3.6 (2.5-5.7)	21 (17-47)	26 (25-62)	38 (37-75)
	1.3	2.5 (1.5-4.5)	3.0 (2.2-5.9)	4.3 (3.2-7.1)	26 (21-59)	32 (31-77)	47 (47-95)
	2	3.2 (2.2-6.4)	3.9 (3.2-8.4)	5.5 (4.6-10.1)	33 (31-84)	46 (40-111)	66 (60-135)
	4	4.0 (3.6-10.1)	5.4 (4.8-13.3)	7.6 (6.7-16.1)	50 (40-134)	76 (49-176)	109 (72-216)
Extremely dense	1	2.0 (1.1-4.3)	2.5 (1.7-5.9)	3.6 (2.4-7.3)	21 (16-57)	26 (24-77)	39 (36-97)
	1.3	2.4 (1.4-5.4)	3.0 (2.1-7.3)	4.3 (3.1-9.1)	25 (20-72)	31 (30-96)	46 (45-122)
	2	3.0 (2.0-7.5)	3.7 (3.0-10.1)	5.3 (4.4-12.6)	31 (29-99)	43 (38-134)	64 (57-170)
	4	3.5 (3.3-11.2)	4.9 (4.3-15.1)	7.3 (6.0-18.9)	46 (36-149)	70 (43-202)	105 (64-257)

Abbreviations: RR, relative risk.

* Life years gained are undiscounted.

† Screening is initiated at age 50.

‡ Women who are currently 65 and have been screened biennially from 50-64.

Statistical Analysis

For each age group modeled (≥50 and ≥65 years), there were 16 possible population subgroups based on combinations of breast cancer risk and density. Benefits and harms for each strategy were compared with no screening for every 1000 women screened. No screening was assumed to occur before age 50 years in all analyses. Screening strategies for women aged 65 to 74 years assumed that they received biennial mammography during ages 50 to 64 years. We report the median benefits and harms and the range across models as a measure of uncertainty. In secondary analyses, the ratio of false-positive mammograms to breast cancer deaths averted was calculated as a metric of the tradeoffs of harms to benefits. We also estimated the incremental costs per QALY for each strategy and population risk–density subgroup. For this estimate, the change in cost was divided by the change in benefit (for example, QALYs) when each more costly screening strategy was compared with the strategy with the next lowest cost within the subgroup. Costs and QALYs were discounted at 3% per year, and QALYs included screening and work-up adjustments. Screening strategies were considered cost-effective with a common threshold of $100 000 per QALY gained (51).

Role of the Funding Source

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

RESULTS

The results of all 3 models illustrate that across intervals and age groups, screening (vs. no screening) (Appendix Table 4, available at www.annals.org) had a greater absolute benefit in terms of breast cancer deaths averted, life-years gained, and QALYs gained among 2 groups of women: those with dense breasts and those at higher RR within each breast density group (Tables 2 and 3). Adjustments for screening harms did not affect the ordering of screening strategies by QALY.

Women Starting Screening at Age 50

For all screening intervals, as risk and breast density increased, the benefits (breast cancer deaths averted, life-years gained, and QALYs gained) of screening increased and the harms (false-positive mammograms and benign biopsy results but not overdiagnosis) decreased with greater risk (Tables 2 to 4).Among average-risk women with fatty breasts (RR, 1.0 or 1.3), biennial screening, compared with no screening, in women aged 50 to 74

Table 3 Lifetime QALY benefits of screening annually, biennially or triennially per 1000 women screened by relative risk, breast density, and age group with and without screening and work-up adjustments.

		QALYs gained with screening and work-up adjustments vs. no screening, median (range across models) *			QALYs gained without screening and work-up adjustments vs. no screening, median (range across models)*		
Density	**RR**	**Triennial**	**Biennial**	**Annual**	**Triennial**	**Biennial**	**Annual**
Ages 50-74†							
Almost entirely fatty	1	32 (21-44)	41 (29-49)	51 (36-51)	37 (26-50)	48 (35-58)	63 (47-66)
	1.3	43 (29-59)	54 (39-66)	69 (50-71)	47 (34-65)	61 (45-75)	80 (61-86)
	2	65 (46-93)	82 (63-105)	106 (81-116)	70 (52-99)	89 (69-114)	118 (93-131)
	4	118 (98-183)	150 (128-209)	194 (168-234)	123 (103-190)	157 (135-217)	206 (180-249)
Scattered fibroglandular	1	36 (35-76)	47 (47-86)	60 (60-92)	43 (43-85)	57 (56-99)	78 (78-115)
	1.3	48 (47-101)	63 (62-114)	82 (81-126)	55 (55-110)	73 (72-127)	99 (98-148)
	2	75 (71-155)	100 (92-178)	132 (123-200)	83 (78-164)	110 (102-190)	149 (140-222)
	4	153 (122-292)	199 (158-336)	264 (212-386)	160 (129-301)	209 (168-349)	280 (228-407)
Heterogeneously dense	1	44 (40-110)	57 (55-126)	75 (73-143)	52 (49-120)	69 (66-141)	95 (94-169)
	1.3	57 (54-143)	74 (74-165)	100 (98-190)	65 (63-153)	85 (85-180)	120 (119-216)
	2	86 (83-215)	114 (108-249)	159 (145-292)	94 (91-225)	125 (119-263)	178 (165-317)
	4	164 (133-384)	220 (173-448)	305 (233-533)	172 (141-394)	230 (184-461)	322 (251-556)
Extremely dense	1	47 (40-131)	62 (54-154)	84 (77-185)	54 (47-140)	71 (64-166)	100 (94-206)
	1.3	60 (54-169)	79 (73-199)	108 (104-240)	67 (61-177)	88 (82-211)	124 (120-261)
	2	85 (83-248)	112 (112-293)	161 (153-358)	92 (90-257)	121 (121-305)	176 (169-379)
	4	154 (129-425)	210 (169-503)	302 (231-622)	161 (136-433)	218 (178-514)	317 (246-641)
Ages 65-74‡							
Almost entirely fatty	1	9 (6-15)	11 (8-18)	15 (11-20)	11 (8-16)	13 (10-21)	19 (15-24)
	1.3	12 (8-19)	15 (11-24)	20 (16-27)	14 (10-21)	17 (14-27)	24 (20-31)
	2	18 (13-30)	22 (19-38)	29 (26-42)	20 (15-31)	24 (21-40)	34 (30-47)
	4	30 (25-55)	37 (36-71)	50 (49-81)	32 (27-57)	39 (38-73)	54 (53-85)
Scattered fibroglandular	1	10 (10-21)	13 (12-27)	18 (17-29)	13 (13-23)	17 (16-30)	24 (23-36)
	1.3	13 (13-28)	18 (16-35)	25 (22-39)	16 (15-30)	22 (19-39)	31 (28-46)
	2	19 (19-42)	28 (23-53)	38 (32-60)	21 (21-44)	31 (26-57)	44 (38-67)
	4	35 (28-75)	52 (33-96)	71 (47-111)	37 (30-77)	55 (37-99)	77 (53-117)
Heterogeneously dense	1	12 (10-35)	15 (14-45)	20 (20-52)	15 (13-38)	19 (18-49)	27 (27-60)
	1.3	15 (13-45)	20 (18-58)	27 (26-68)	18 (16-47)	24 (22-62)	35 (33-76)
	2	21 (20-65)	30 (25-85)	43 (36-100)	24 (23-67)	34 (29-89)	50 (43-108)
	4	35 (27-105)	54 (33-138)	76 (46-167)	38 (30-107)	57 (36-142)	82 (52-174)
Extremely dense	1	12 (10-44)	15 (15-58)	21 (21-72)	15 (12-46)	18 (18-62)	27 (27-78)
	1.3	15 (13-55)	20 (18-74)	28 (27-91)	18 (15-57)	23 (21-77)	34 (32-98)
	2	20 (20-78)	29 (24-104)	43 (35-130)	22 (22-80)	32 (27-107)	48 (41-136)
	4	33 (24-118)	51 (29-159)	76 (43-201)	35 (26-120)	53 (32-162)	80 (47-206)

Abbreviations: QALY, quality-adjusted life year; RR, relative risk.

* QALYs gained are undiscounted.

† Screening is initiated at age 50.

‡ Women who are currently 65 and have been screened biennially from 50-64.

Table 4 Lifetime harms of screening annually, biennially or triennially per 1000 women screened by relative risk, breast density, and age group

Density and RR	False-positives vs. no screening, median (range across models)		
	Triennial	Biennial	Annual
Ages 50-74†			
Almost entirely fatty			
1	489 (424-616)	618 (613-858)	1101 (1094-1548)
1.3	484 (420-611)	612 (606-851)	1089 (1081-1536)
2	471 (412-600)	598 (590-836)	1062 (1051-1507)
4	438 (390-571)	564 (547-794)	996 (972-1429)
Scattered areas of fibroglandular density			
1	781 (693-935)	1009 (991-1326)	1806 (1776-2440)
1.3	767 (683-922)	994 (972-1309)	1776 (1740-2406)
2	734 (662-894)	963 (929-1267)	1714 (1659-2329)
4	649 (613-818)	888 (818-1158)	1568 (1452-2123)
Heterogeneously dense			
1	917 (822-1064)	1197 (1171-1524)	2123 (2080-2829)
1.3	894 (807-1043)	1174 (1141-1493)	2078 (2023-2771)
2	842 (775-995)	1125 (1073-1424)	1984 (1896-2642)
4	715 (703-875)	1016 (906-1248)	1778 (1585-2308)
Extremely dense			
1	732 (652-849)	939 (925-1200)	1668 (1647-2225)
1.3	712 (638-827)	917 (898-1169)	1626 (1597-2167)
2	666 (608-780)	872 (839-1102)	1540 (1487-2039)
4	555 (543-663)	776 (697-933)	1359 (1223-1719)
Ages 65-74‡			
Almost entirely fatty			
1	145 (137-169)	209 (206-227)	413 (395-459)
1.3	142 (135-166)	206 (202-224)	405 (388-453)
2	135 (130-160)	198 (193-217)	387 (373-438)
4	119 (118-145)	178 (169-197)	340 (335-399)
Scattered areas of fibroglandular density			
1	230 (225-278)	343 (333-375)	667 (648-757)
1.3	223 (220-271)	335 (322-366)	645 (632-741)
2	209 (206-257)	317 (298-348)	597 (597-704)
4	180 (166-225)	276 (239-299)	520 (480-607)
Heterogeneously dense			
1	273 (260-329)	407 (397-432)	794 (760-875)
1.3	262 (250-319)	394 (381-417)	762 (735-845)
2	238 (230-298)	367 (346-384)	693 (684-779)
4	182 (181-254)	302 (264-311)	580 (528-617)

Benign biopsies vs. no screening, median (range across models)			Over-diagnosis vs. no screening, median (range across models)*		
Triennial	**Biennial**	**Annual**	**Triennial**	**Biennial**	**Annual**
79 (68-106)	91 (91-136)	127 (127-191)	11 (9-17)	12 (11-20)	17 (12-24)
78 (67-106)	91 (90-135)	126 (125-190)	12 (11-21)	15 (11-26)	21 (12-31)
76 (66-104)	89 (88-133)	123 (122-187)	17 (11-31)	22 (11-37)	30 (12-44)
71 (63-99)	84 (81-126)	116 (113-177)	27 (11-53)	35 (11-63)	49 (12-75)
126 (111-158)	150 (147-206)	209 (206-296)	13 (11-22)	17 (11-27)	23 (12-35)
123 (110-156)	148 (144-203)	206 (202-292)	16 (11-28)	20 (11-34)	29 (12-44)
118 (107-152)	143 (138-197)	199 (193-283)	21 (10-39)	28 (11-48)	39 (12-62)
105 (99-140)	132 (122-181)	183 (169-259)	31 (11-60)	40 (12-74)	56 (13-95)
163 (146-195)	178 (174-235)	266 (261-365)	16 (10-20)	20 (11-26)	28 (12-38)
159 (144-191)	174 (169-230)	261 (254-358)	19 (10-25)	24 (11-32)	34 (12-46)
150 (138-183)	167 (160-220)	249 (238-342)	25 (10-34)	32 (11-44)	45 (13-63)
128 (126-162)	152 (136-194)	224 (200-301)	32 (11-49)	41 (12-63)	57 (14-89)
130 (116-156)	139 (137-185)	209 (206-288)	16 (10-17)	21 (11-22)	31 (12-32)
127 (113-152)	136 (133-181)	204 (200-281)	19 (10-21)	26 (11-27)	37 (12-39)
119 (108-144)	129 (125-171)	193 (186-265)	26 (10-26)	34 (11-35)	47 (13-53)
99 (97-123)	116 (104-146)	171 (154-225)	32 (10-37)	41 (12-49)	56 (15-74)
22 (20-25)	29 (29-32)	45 (43-51)	5 (4-8)	6 (5-11)	9 (5-13)
21 (20-25)	29 (28-31)	45 (43-50)	7 (4-10)	8 (5-14)	11 (5-17)
20 (20-24)	28 (27-30)	43 (41-48)	9 (4-15)	11 (5-20)	15 (6-25)
18 (18-22)	25 (24-28)	37 (37-44)	14 (5-25)	16 (6-34)	22 (7-41)
34 (34-42)	48 (47-52)	73 (71-83)	7 (4-10)	8 (5-15)	12 (5-20)
33 (33-41)	47 (45-51)	71 (69-81)	8 (4-13)	10 (5-19)	14 (6-24)
31 (31-39)	44 (42-49)	66 (66-77)	11 (5-18)	13 (6-26)	18 (6-34)
27 (25-34)	39 (33-42)	57 (53-67)	14 (5-27)	17 (7-38)	23 (8-50)
46 (44-56)	57 (56-61)	95 (91-105)	8 (4-10)	10 (5-14)	14 (6-20)
45 (43-54)	55 (53-58)	91 (88-101)	10 (5-12)	12 (6-17)	17 (7-25)
41 (39-51)	51 (48-54)	83 (82-93)	12 (5-16)	15 (7-23)	21 (8-33)
31 (31-43)	42 (37-44)	70 (63-74)	13 (6-22)	16 (8-32)	22 (10-46)

Table 4 Lifetime harms of screening annually, biennially or triennially per 1000 women screened by relative risk, breast density, and age group (continued)

Density and RR	False-positives vs. no screening, median (range across models)		
	Triennial	Biennial	Annual
Extremely dense			
1	202 (187-239)	295 (291-312)	583 (553-631)
1.3	193 (179-231)	284 (279-298)	559 (532-604)
2	175 (161-214)	263 (253-268)	507 (491-544)
4	133 (118-180)	197 (191-221)	404 (383-412)

Abbreviations: RR, relative risk.
* Over-diagnosed cases are defined as cases that would not have been clinically detected in the absence of screening. The value includes DCIS and invasive over-diagnosis. Over-diagnosis is calculated by comparing cases detected in the screening scenario to those detected in the unscreened scenario.
† Per 1000 women compared to no screening at any age.
‡ Per 1000 women compared to biennial mammograms 50-64 with no subsequent screening.

years averted a median of 4.1 and 5.3 breast cancer deaths per 1000 women screened, respectively. In average-risk women with scattered fibroglandular density (RR, 1.0 or 1.3), biennial screening compared with no screening averted a median of 5.2 and 6.5 breast cancer deaths, respectively (Table 2). Screening outcomes were similar for triennial screening compared with no screening in average-risk women with low-breast density; for every 1000 women screened, the median number of breast cancer deaths averted ranged from 3.4 to 5.1. Screening triennially compared with biennially for average-risk women with low breast density resulted in a median ranging from 21% to 23% fewer false-positive mammograms, 13% to 17% fewer benign biopsies, and 8% to 20% fewer overdiagnosed cases (Table 4). Among women with fatty breasts (RR, 2.0), triennial screening, compared with biennial screening, averted a median of 1.6 breast cancer deaths per 1000 screened. In women with scattered fibroglandular density (RR, 2.0), triennial screening, compared with biennial screening, averted 2 breast cancer deaths per 1000 women screened. Thus, 1000 women with fatty breasts (RR, 2.0) and 1000 women with scattered fibroglandular density (RR, 2.0) would have 9 rounds of triennial screening resulting in 6.4 and 7.2 breast cancer deaths averted, 471 and 734 false-positive mammograms, and 76 and 118 biopsy results, respectively; for 13 rounds of biennial screening, we noted 8.0 and 9.2 breast cancer deaths averted, 598 and 963 false-positive mammograms, and 89 and 143 biopsy results, respectively.

The benefits of more frequent screening increased as density increased and RR increased to 2 or greater. For example, biennial screening, compared with no screening, among women aged 50 to 74 years in subgroups with an RR of 2 and heterogeneously dense breasts resulted in a median of 10.6 breast cancer deaths averted and 1125

Benign biopsies vs. no screening, median (range across models)			Over-diagnosis vs. no screening, median (range across models)*		
Triennial	**Biennial**	**Annual**	**Triennial**	**Biennial**	**Annual**
34 (32-41)	41 (41-44)	70 (66-76)	7 (4-9)	10 (6-11)	15 (7-17)
33 (30-39)	40 (39-42)	67 (64-72)	9 (5-10)	12 (6-13)	18 (7-20)
30 (27-36)	37 (35-37)	61 (59-65)	12 (5-12)	15 (7-17)	21 (9-27)
23 (20-31)	28 (27-31)	49 (46-49)	12 (6-16)	14 (9-24)	20 (11-38)

false-positive mammograms per 1000 women screened. If these women received annual rather than biennial screening, a median of 3.7 more deaths could have been averted; however, false-positive mammograms would increase almost 2-fold (1984 vs. 1125 false-positive mammograms per 1000 women screened). Breast cancer deaths averted per

1000 women screened were highest with annual screening for women ages 50 to 74 years with all levels of breast density and an RR of 4.0; averted deaths ranged from 17.2 in women with fatty breasts to 20.5 in women with extremely dense breasts.

The Figure (top) is an exemplar model showing the ratio of harms and benefits for subgroups of women with different levels of risk and density screened from ages 50 to 74 years. Compared with the ratios projected for biennial screening of average-risk women from ages 50 to 74 years regardless of breast density, annual screening has a similar or better ratio when the RR is 2 or greater across all density groups. Triennial screening has similar or better ratios of harms and benefits than biennial screening for average-risk women regardless of breast density in nearly all of the RR and density subgroups because false-positive mammograms are reduced with triennial screening, and the magnitude of breast cancer deaths averted is similar or slightly lower than with biennial screening.

Women at Age 65

The different intervals among women aged 65 to 74 years had similar patterns of benefits and harms across subgroups as observed for screening during ages 50 to 74 years but with lower absolute magnitudes (Tables 2 to 4 and Figure, bottom). If women changed from biennial to triennial screening at age 65 years, fewer than a median of 1 less death per 1000 women screened was averted for all RRs and density subgroups. The exception was women with an RR of 4 and heterogeneously or extremely dense breasts; a median of 1.4 fewer breast cancer deaths were averted in this group (Table 2). For example, continuing biennial screening among average-risk women (RR, 1.0 or 1.3) and women with fatty breasts or scattered fibroglandular density averted a median of 1.8 to 2.3 deaths for women with fatty breasts and 2.1 to 2.6 deaths for women with scattered fibroglandular density for every 1000 women screened (Table 2); switching to triennial

Table 5 Incremental costs per quality-adjusted life year gained* by breast density, risk level, screening interval, and age for 3 models.

Density	RR	Screening Frequency	Age 50-74			Age 65-74		
			Model E	Model W	Model GE	Model E	Model W	Model GE
Fatty	1.0	Triennial	**68,777**	117,753	**43,098**	100,058	131,294	**27,639**
		Biennial	122,007	123,132	232,710	109,587	212,665	104,235
		Annual	389,195	586,116	Dom	435,881	516,979	>1,000,000
	1.3	Triennial	**50,231**	**83,220**	**27,022**	**70,716**	**92,938**	**15,785**
		Biennial	**83,577**	**86,426**	133,826	**75,433**	135,221	**67,152**
		Annual	231,495	309,654	>1,000,000	258,193	286,643	799,501
	2.0	Triennial	**30,910**	W Dom	**10,364**	**42,229**	**58,276**	**3,004**
		Biennial	**50,526**	**50,084†**	**65,297**	**46,300**	**70,911**	**32,912**
		Annual	122,540	148,375	392,745	141,183	146,961	263,493
	4.0	Triennial	**14,969**	**22,663**	†	**19,130**	W Dom	†
		Biennial	**22,802**	**23,295**	**19,932**	**21,242**	**30,054**	**5,331**
		Annual	**54,906**	**56,451**	**95,362**	**69,089**	**62,251**	**76,840**
Scat-tered	1.0	Triennial	**69,714**	**72,156**	**18,509**	W Dom	**55,051**	**14,112**
		Biennial	111,605	**75,673**	104,454	101,612	Dom	**61,723**
		Annual	317,991	288,199	Dom	382,578	612,349	>1,000,000
	1.3	Triennial	**50,010**	**51,493**	**9,683**	W Dom	**60,785**	**5,449**
		Biennial	**75,416**	**53,967**	**63,057**	**72,488**	**73,479**	**39,636**
		Annual	186,322	171,038	488,376	224,322	201,088	450,818
	2.0	Triennial	**31,053**	**29,757**	**641**	W Dom	**38,299**	†
		Biennial	**43,721**	**31,198**	**28,182**	**42,160**	**42,347**	**15,956**
		Annual	**96,584**	**85,607**	144,723	120,188	104,553	159,293
	4.0	Triennial	**15,414**	**12,179**	†	W Dom	**17,507**	Dom
		Biennial	**19,733**	**13,116**	**5,116**	**20,076**	**17,977**	‡
		Annual	**44,019**	**32,452**	**39,105**	**61,818**	**39,362**	**42,660**
Het. dense	1.0	Triennial	**57,924**	W Dom	**8,016**	W Dom	**75,197**	**611**
		Biennial	**85,241**	**60,333†**	**50,421**	**85,145**	**96,863**	**23,104**
		Annual	222,789	185,805	268,798	279,586	290,534	179,689
	1.3	Triennial	**42,324**	**41,815**	**2,179**	**60,235**	**54,355**	†
		Biennial	**61,309**	**42,551**	**31,442**	**61,760**	**60,225**	**11,809**
		Annual	137,983	116,700	134,915	169,196	174,243	97,850
	2.0	Triennial	**26,726**	**23,375**	†	W Dom	**31,637**	†
		Biennial	**35,235**	**26,574**	**12,543**	**36,446**	**36,762**	**478**
		Annual	**75,747**	**57,557**	**56,331**	**99,035**	**85,503**	**44,784**
	4.0	Triennial	**13,432**	**8,534**	Dom	W Dom	**13,298**	Dom
		Biennial	**16,745**	**9,256**	‡	**18,673**	**13,814**	‡
		Annual	**36,845**	**22,339**	**14,716**	**57,264**	**32,355**	**8,752**
Dense	1.0	Triennial	**50,563**	**52,953**	**3,017**	W Dom	**63,918**	†
		Biennial	**68,216**	**55,420**	**27,942**	**75,917**	**77,061**	**8,555**

Table 5 Incremental costs per quality-adjusted life year gained* by breast density, risk level, screening interval, and age for 3 models. (continued)

Density	RR	Screening Frequency	Age 50-74			Age 65-74		
			Model E	Model W	Model GE	Model E	Model W	Model GE
		Annual	148,014	129,536	89,425	187,329	203,860	60,177
	1.3	Triennial	**37,937**	**36,486**	†	W Dom	**45,929**	†
		Biennial	**49,172**	**40,051**	**16,293**	**55,033**	**52,754**	**2,547**
		Annual	101,399	**87,230**	**56,264**	130,774	130,339	**36,740**
	2.0	Triennial	**24,715**	**20,626**	†	W Dom	**26,367**	Dom
		Biennial	**30,291**	**23,683**	**4,631**	**35,097**	**32,766**	‡
		Annual	**60,577**	**47,687**	**25,753**	**82,794**	**71,187**	**15,070**
	4.0	Triennial	**13,169**	**7,130**	Dom	W Dom	**10,180**	Dom
		Biennial	**14,856**	**7,823**	‡	**19,207**	**11,669**	Dom
		Annual	**31,433**	**18,224**	**4,407**	**52,645**	**26,834**	§

Note: Incremental ratios **bold** if values are <$100,000, a common threshold for least costly and most effective strategies (dominant). Unless otherwise indicated, triennial strategies are compared to no screening. Breast density categories shown as: fatty, almost entirely fat; scattered, scattered fibroglandular density; het. dense, heterogeneously dense; and dense, extremely dense.
Abbreviations: RR, relative risk; Dom, more expensive and less effective (strongly dominated); W Dom, more expensive and more effective but less efficient (weakly dominated).
*Costs and quality-adjusted life years discounted at 3% per year. Quality-adjusted life years include disutility from participation in screening mammography.
†Strategy with no screening is strongly dominated. Triennial is the least costly strategy for comparison.
‡Strategy with biennial screening is the least costly.
§Strategy with annual screening is the least costly

screening averted a median of 1.5 to 1.9 deaths for women with fatty breasts and 1.7 to 2.1 deaths for women with scattered fibroglandular density. Switching from biennial to annual screening increased the median number of breast cancer deaths averted to 2 or more for women with heterogeneously or extremely dense breasts and an RR of 4.

As was the case for screening in women aged 50 to 74 years, the ratio of harms (measured as false-positive mammograms) and benefits (breast cancer deaths averted) for annual screening in women aged 65 to 74 years was similar to or better (lower) than that seen in biennial screening of average-risk women with an RR of 2 or greater in all density subgroups; exceptions were rare (Figure, bottom). Triennial screening also had a lower or more favorable ratio than biennial screening because it reduces false-positive mammograms, and the magnitude of breast cancer deaths averted is the same or slightly lower. Continuing biennial screening has a similar balance as triennial screening for most subgroups as seen for average-risk groups, regardless of breast density

Cost-Effectiveness

When we used a common threshold of $100 000 per QALY, triennial strategies were the only costeffective strategies for subgroups with average risk and low breast density (fatty breasts or scattered fibroglandular density) in both age groups (Table 5). Biennial strategies were cost-effective for most density subgroups at average or intermediate risk (RR, 1.3 or 2.0). Annual strategies were only consistently cost-effective across models for subgroups with an RR of 4, regardless of density, or an RR of 2 or greater and heterogeneously or extremely dense breasts.

DISCUSSION

This collaborative modeling study shows that risk and density level can be useful for guiding tailored screening recommendations. For average-risk women in low-density subgroups, which comprise a large proportion of the population, triennial screening provides a reasonable balance of benefits and harms and is costeffective. Annual screening has a favorable balance of benefits and harms and would be considered costeffective for subgroups of women aged 50 years with risk levels that are 2 to 4 times the average and that have heterogeneously or extremely dense breasts. Benefits of screening women with heterogeneously dense breasts (at any interval) were greater than screening those with extremely dense breasts at each risk level, reflecting increased risk but fewer missed cases of cancer than screening women with extremely dense breasts. The same patterns are seen for women aged 65 years such that subgroups at average risk with low breast density can consider triennial screening. In contrast, the few women who remain at higher risk might benefit from annual screening. Of note, biennial screening maintains an acceptable balance of outcomes and is also cost-effective for women with an RR of 1.3 or 2 as long as they are not in the highest-density groups. Screening benefits and harms exist on a continuum across age, risk, and density, with the optimal screening interval depending on women's values and preferences for benefits and harms.

Current U.S. screening guidelines focus on the average-risk population and generally recommend biennial screening for women in their 50s or older (3, 4). These new modeling results support this recommendation for women who do not have either higher-than average risk and high breast density or average to low risk and low breast density. Annual screening has been suggested for high-risk women (4). The current results provide further guidance on the specific combinations of RRs and breast density after age 50 years that identify the subgroups in which annual screening should be considered; these subgroups are estimated to constitute fewer than 1% of the population at both ages 50 and 65 years (BCSC; Miglioretti DL. Personal communication. 2016).

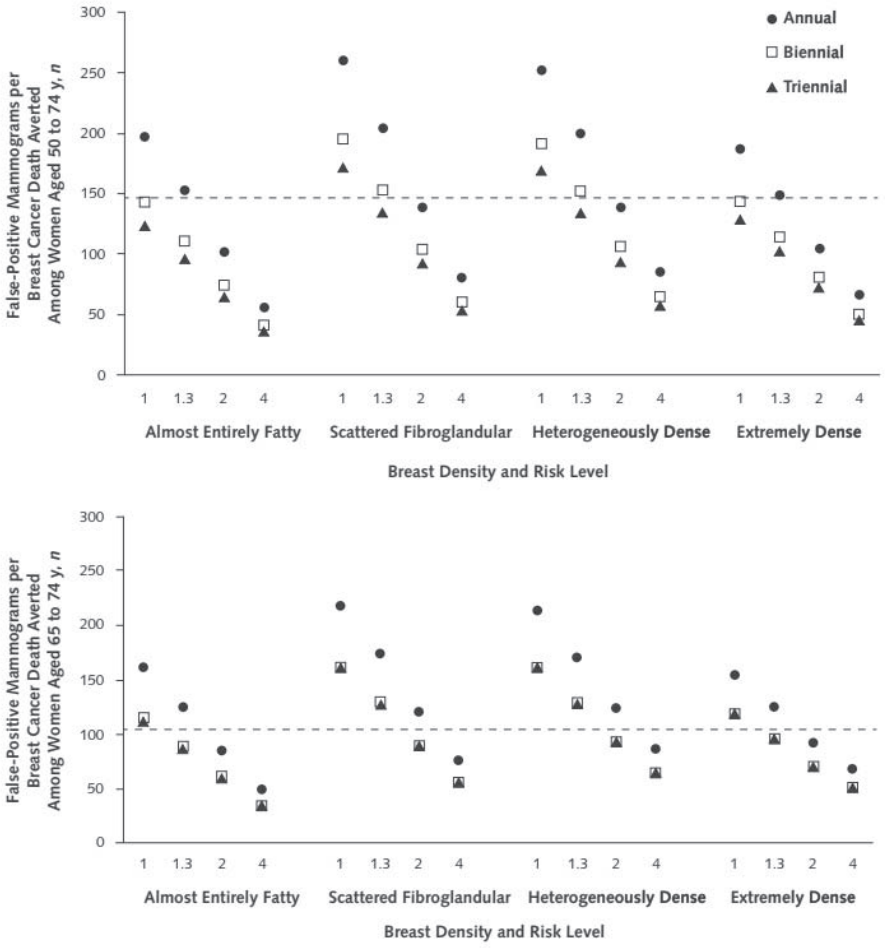


Figure 1 False-positives mammograms per breast cancer death averted for women (A) aged 50-74 and (B) aged 65-74 according to screening frequency and risk level (relative risk group, breast density) using an exemplar model (Model E). Values for all screening frequencies compared to the scenario with no mammography screening. Values for ages 65-74 assume all women received biennial screening during ages 50-64. Dashed lines show this value for women with average density and average risk receiving biennial screening (147.7 for ages 50-74 and 105.8 for ages 65-74). Having fewer false-positives per death averted than this level, i.e., a value below the dashed line, would be more favorable.

Although triennial screening is routinely used in several countries (52, 53), this interval has not been considered in the United States. Our modeling suggests that triennial screening has a similar balance of benefits and harms compared with biennial screening in some groups. Decisions about using triennial versus biennial screening for average-risk women in the lowdensity subgroups result in fewer false-positive mammograms,

biopsies, and overdiagnosis with minimal effect on breast cancer deaths averted. Others have noted that triennial screening can be cost-effective for average-risk women or those with an RR of 2 or less aged 60 to 79 years with fatty breasts or scattered fibroglandular density(10, 11). We found that 12% of women aged 50 years and 20% of those aged 65 years have low breast density (fatty breasts and scattered fibroglandular density) and an RR of 1.0 or 1.3 (BCSC; Miglioretti DL. Personal communication. 2016).

Breast cancer screening guidelines include an upper limit based on age or life expectancy (3, 4, 54). Although we did not evaluate comorbidity, our study results suggest that screening intervals for older women should be based on competing causes of mortality, breast cancer risk, and changes in breast density associated with aging. The ability to tailor screening based on density may become increasingly feasible with the trend toward mandated standard reporting of breast density to women after a mammogram. Because our results show that the RR of breast cancer in combination with breast density has a strong influence on the net benefit of mammography at all screening intervals, evaluation of different risk assessment tools will be important in this context.

Although the models provide new data and have consistent conclusions, several caveats should be considered. First, the 3 models used common inputs but varied in how these data were implemented based on model structure. These variations led to differences in the absolute values for outcome metrics. For example, based on assumptions about temporal trends in underlying incidence, models with the lowest projected incidence estimate fewer breast cancer deaths averted than those with higher incidence. This analysis includes 3 of 6 Cancer Intervention and Surveillance Modeling Network breast models and is an extension of work conducted by all 6 groups(8). Second, because the analytic goal was to determine screening efficacy, the models assumed 100% adherence to screening and use of the most effective modern treatments. Actual benefits will fall short of those projected under these assumptions. Third, we did not explicitly consider lower-than-average risk (that is, RR <1). It will be important to extend our analyses to lower-risk groups because most U.S. women have an RR less than 1 across all density subgroups (70% of women aged 50 years and 66% aged 65 years) (BCSC; Miglioretti DL. Personal communication. 2016). By extension, our current findings suggest that triennial screening would be a reasonable option for lower-than-average risk women with fatty breasts or scattered fibroglandular density. Fourth, we did not model the effect of screening from ages 40 to 49 years, other combinations of ages and intervals, or carriers of breast cancer susceptibility genes 1 and 2. Whether the lack of strategies incorporating screening women in their 40s would affect the balance of benefits and harms against longer (or shorter) screening intervals after age 50 years is unclear. Fifth, although 2 age groups and change in density between age groups were considered, our results do not provide guidance for women whose risk changes over time; modeling change in risk with aging is an important area for future research. Sixth, we used RR rather than absolute risk

level because our simulation models were better suited for this approach. Absolute risk calculators are commonly available (27, 55-57), and the suitability of these calculators to assign risk to personalize screening intervals should continue to be evaluated. Finally, we did not evaluate alternative or supplemental imaging.

Overall, this comparative modeling study illustrates consistent patterns in benefits and harms that could be useful for guiding shared decision making and tailoring screening intervals. The results show that for all screening intervals, benefits and harms change with risk and breast density. Further, the threshold to decide on the screening interval will depend on individual preference(1). Assessing breast density and breast cancer risk can identify subgroups of average-risk women with low breast density who can consider triennial screening and higher-risk women with high breast density who may benefit from annual screening.

Reproducible Research Statement: *Study protocol*: Not available. *Statistical code*: Detailed information about the models is available online at http://cisnet.cancer.gov/breast/profiles.html and in reference (14). *Data set*: Input and output data from the models are available at reference (14) and by contacting Dr. Trentham-Dietz at trentham@wisc.edu.

REFERENCES

1. Kerlikowske K. Progress Toward Consensus on Breast Cancer Screening Guidelines and Reducing Screening Harms. JAMA Intern Med. 2015;175(12):1970-1.
2. Siu AL, Bibbins-Domingo K, Grossman DC, LeFevre ML, Force USPST. Convergence and Divergence Around Breast Cancer Screening. Ann Intern Med. 2016;164(4):301-2.
3. Siu AL, Force USPST. Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med. 2016;164(4):279-96.
4. Oeffinger KC, Fontham ET, Etzioni R, Herzig A, Michaelson JS, Shih YC, et al. Breast Cancer Screening for Women at Average Risk: 2015 Guideline Update From the American Cancer Society. JAMA. 2015;314(15):1599-614.
5. Myers ER, Moorman P, Gierisch JM, Havrilesky LJ, Grimm LJ, Ghate S, et al. Benefits and Harms of Breast Cancer Screening: A Systematic Review. JAMA. 2015;314(15):1615-34.
6. Nelson HD, Pappas M, Cantor A, Griffin J, Daeges M, Humphrey L. Harms of Breast Cancer Screening: Systematic Review to Update the 2009 U.S. Preventive Services Task Force Recommendation. Ann Intern Med. 2016;164(4):256-67.
7. Lauby-Secretan B, Scoccianti C, Loomis D, Benbrahim-Tallaa L, Bouvard V, Bianchini F, et al. Breast-cancer screening--viewpoint of the IARC Working Group. N Engl J Med. 2015;372(24):2353-8.
8. Mandelblatt JS, Stout NK, Schechter CB, van den Broek JJ, Miglioretti DL, Krapcho M, et al. Collaborative Modeling of the Benefits and Harms Associated With Different U.S. Breast Cancer Screening Strategies. Ann Intern Med. 2016;164(4):215-25.
9. Kerlikowske K, Zhu W, Hubbard RA, Geller B, Dittus K, Braithwaite D, et al. Outcomes of screening mammography by frequency, breast density, and postmenopausal hormone therapy. JAMA Intern Med. 2013;173(9):807-16.
10. Vilaprinyo E, Forne C, Carles M, Sala M, Pla R, Castells X, et al. Cost-effectiveness and harm-benefit analyses of risk-based screening strategies for breast cancer. PloS one. 2014;9(2):e86858.
11. Schousboe JT, Kerlikowske K, Loh A, Cummings SR. Personalizing mammography by breast density and other risk factors for breast cancer: analysis of health benefits and cost-effectiveness. Annals of Internal Medicine. 2011;155(1):10-20.
12. Kerlikowske K, Zhu W, Tosteson AN, Sprague BL, Tice JA, Lehman CD, et al. Identifying women with dense breasts at high risk for interval cancer: a cohort study. Ann Intern Med. 2015;162(10):673-81.
13. van Ravesteyn NT, Miglioretti DL, Stout NK, Lee SJ, Schechter CB, Buist DS, et al. Tipping the Balance of Benefits and Harms to Favor Screening Mammography Starting at Age 40 Years: A Comparative Modeling Study of Risk. Annals of Internal Medicine. 2012;156(9):609-17.
14. Mandelblatt J, Cronin KA, De Koning H, Miglioretti DL, Schechter C, Stout N, et al. Collaborative Modeling of U.S. Breast Cancer Screening Strategies. Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services, Rockville, MD; AHRQ Publication No. 14-05201-EF-4, December 2015. Available from: http://www.uspreventiveservicestaskforce.org/Home/GetFile/1/16255/collabmodelingbc/pdf. Accessed May 2016.
15. Breast Cancer Surveillance Consortium [Internet]. Rockville, MD: National Cancer Institute [2015 Jul 06; cited 2016 May

17]. Available from: http://breastscreening.cancer.gov.
16. American College of Radiology. The American College of Radiology Breast Imaging Reporting and Data System (BI-RADS). 4th ed. Reston, VA: American College of Radiology; 2003.
17. Munsell MF, Sprague BL, Berry DA, Chisholm G, Trentham-Dietz A. Body mass index and breast cancer risk according to postmenopausal estrogen-progestin use and hormone receptor status. Epidemiol Rev. 2014;36(1):114-36.
18. Collaborative Group on Hormonal Factors in Breast Cancer. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. Lancet Oncol. 2012;13(11):1141-51.
19. Hamajima N, Hirose K, Tajima K, Rohan T, Calle EE, Heath CW, Jr., et al. Alcohol, tobacco and breast cancer--collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. Br J Cancer. 2002;87(11):1234-45.
20. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Alcohol Consumption and Ethyl Carbamate. Lyon, France: World Health Organization; 2010.
21. Chlebowski RT, Anderson GL, Aragaki AK, Prentice R. Breast Cancer and Menopausal Hormone Therapy by Race/Ethnicity and Body Mass Index. J Natl Cancer Inst. 2016;108(2).
22. Chlebowski RT, Anderson GL, Gass M, Lane DS, Aragaki AK, Kuller LH, et al. Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. JAMA. 2010;304(15):1684-92.
23. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results. From the Women's Health Initiative randomized controlled trial. JAMA. 2002;288(3):321-33.
24. Trentham-Dietz A, Sprague BL, Hampton JM, Miglioretti DL, Nelson HD, Titus LJ, et al. Modification of breast cancer risk according to age and menopausal status: a combined analysis of five population-based case-control studies. Breast Cancer Res Treat. 2014;145(1):165-75.
25. Collaborative Group on Hormonal Factors in Breast Cancer. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease. Lancet. 2001;358(9291):1389-99.
26. Pharoah PD, Day NE, Duffy S, Easton DF, Ponder BA. Family history and the risk of breast cancer: a systematic review and meta-analysis. Int J Cancer. 1997;71(5):800-9.
27. Tice JA, Miglioretti DL, Li CS, Vachon CM, Gard CC, Kerlikowske K. Breast Density and Benign Breast Disease: Risk Assessment to Identify Women at High Risk of Breast Cancer. J Clin Oncol. 2015;33(28):3137-43.
28. Dyrstad SW, Yan Y, Fowler AM, Colditz GA. Breast cancer risk associated with benign breast disease: systematic review and meta-analysis. Breast Cancer Res Treat. 2015;149(3):569-75.
29. Mavaddat N, Pharoah PD, Michailidou K, Tyrer J, Brook MN, Bolla MK, et al. Prediction of breast cancer risk based on profiling with common genetic variants. J Natl Cancer Inst. 2015;107(5).
30. Munoz D, Near AM, van Ravesteyn NT, Lee SJ, Schechter CB, Alagoz O, et al. Effects of screening and systemic adjuvant therapy on ER-specific US breast

cancer mortality. J Natl Cancer Inst. 2014;106(11).
31. Gangnon RE, Sprague BL, Stout NK, Alagoz O, Weedon-Fekjaer H, Holford TR, et al. The contribution of mammography screening to breast cancer incidence trends in the United States: an updated age-period-cohort model. Cancer Epidemiol Biomarkers Prev. 2015;24(6):905-12.
32. Carter SB, Gartner SS, Haines MR, Olmstead AL, Sutch R, Wright G. Historical Statistics of the United States, Volume One: Population. New York: Cambridge University Press; 2006.
33. Fryback DG, Stout NK, Rosenberg MA, Trentham-Dietz A, Kuruchittham V, Remington PL. The Wisconsin Breast Cancer Epidemiology Simulation Model. J Natl Cancer Inst Monogr. 2006(36):37-47.
34. Mandelblatt J, Schechter CB, Lawrence W, Yi B, Cullen J. The SPECTRUM population model of the impact of screening and treatment on U.S. breast cancer trends from 1975 to 2000: principles and practice of the model methods. J Natl Cancer Inst Monogr. 2006(36):47-55.
35. Tan SY, van Oortmarssen GJ, de Koning HJ, Boer R, Habbema JD. The MISCAN-Fadia continuous tumor growth model for breast cancer. J Natl Cancer Inst Monogr. 2006(36):56-65.
36. Nelson HD, Zakher B, Cantor A, Fu R, Griffin J, O'Meara ES, et al. Risk factors for breast cancer for women aged 40 to 49 years: a systematic review and meta-analysis. Ann Intern Med. 2012;156(9):635-48.
37. Cronin KA, Mariotto AB, Clarke LD, Feuer EJ. Additional common inputs for analyzing impact of adjuvant therapy and mammography on U.S. mortality. J Natl Cancer Inst Monogr. 2006(36):26-9.
38. Cronin KA, Yu B, Krapcho M, Miglioretti DL, Fay MP, Izmirlian G, et al. Modeling the dissemination of mammography in the United States. Cancer Causes Control. 2005;16(6):701-12.
39. Early Breast Cancer Trialists' Collaborative Group, Peto R, Davies C, Godwin J, Gray R, Pan HC, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet. 2012;379(9814):432-44.
40. Mariotto AB, Feuer EJ, Harlan LC, Abrams J. Dissemination of adjuvant multiagent chemotherapy and tamoxifen for breast cancer in the United States using estrogen receptor information: 1975-1999. J Natl Cancer Inst Monogr. 2006(36):7-15.
41. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. 2015.
42. Stout NK, Lee SJ, Schechter CB, Kerlikowske K, Alagoz O, Berry D, et al. Benefits, harms, and costs for breast cancer screening after US implementation of digital mammography. J Natl Cancer Inst. 2014;106(6):dju092.
43. Yabroff KR, Lamont EB, Mariotto A, Warren JL, Topor M, Meekins A, et al. Cost of care for elderly cancer patients in the United States. J Natl Cancer Inst. 2008;100(9):630-41.
44. de Haes JC, de Koning HJ, van Oortmarssen GJ, van Agt HM, de Bruyn AE, van Der Maas PJ. The impact of a breast cancer screening programme on quality-adjusted life-years. Int J Cancer. 1991;49(4):538-44.
45. Hanmer J, Lawrence WF, Anderson JP, Kaplan RM, Fryback DG. Report of nationally representative values for the noninstitutionalized US adult population for 7 health-related quality-of-life scores. Med Decis Making. 2006;26(4):391-400.
46. Stout NK, Rosenberg MA, Trentham-Dietz A, Smith MA, Robinson SM, Fryback DG. Retrospective cost-effectiveness

analysis of screening mammography. J Natl Cancer Inst. 2006;98(11):774-82.
47. Surveillance Epidemiology and End Results (SEER) Program. (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 9 Regs Research Data, Nov 2014 Sub (1973-2012) <Katrina/Rita Population Adjustment> - Linked to County Attributes - Total U.S., 1969-2013 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2015, based on the November 2014 submission. .
48. Sprague BL, Gangnon RE, Burt V, Trentham-Dietz A, Hampton JM, Wellman RD, et al. Prevalence of mammographically dense breasts in the United States. J Natl Cancer Inst. 2014;106(10).
49. Rosenberg RD, Yankaskas BC, Abraham LA, Sickles EA, Lehman CD, Geller BM, et al. Performance benchmarks for screening mammography. Radiology. 2006;241(1):55-66.
50. van Ravesteyn NT, Stout NK, Schechter CB, Heijnsdijk EA, Alagoz O, Trentham-Dietz A, et al. Benefits and harms of mammography screening after age 74 years: model estimates of overdiagnosis. J Natl Cancer Inst. 2015;107(7).
51. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness--the curious resilience of the $50,000-per-QALY threshold. N Engl J Med. 2014;371(9):796-7.
52. Giordano L, von Karsa L, Tomatis M, Majek O, de Wolf C, Lancucki L, et al. Mammographic screening programmes in Europe: organization, coverage and participation. J Med Screen. 2012;19 Suppl 1:72-82.
53. Von Karsa L, Antilla A, Ronco G, Ponti A, Malila N, Arbyn M, et al. Cancer Screening in the European Union: Report on the implementation of the Council Recommendation on cancer screening. First Report. European Communities; 2008.
54. Lansdorp-Vogelaar I, Gulati R, Mariotto AB, Schechter CB, de Carvalho TM, Knudsen AB, et al. Personalizing age of cancer screening cessation based on comorbid conditions: model estimates of harms and benefits. Ann Intern Med. 2014;161(2):104-12.
55. Gail MH, Brinton LA, Byar DP, Corle DK, Green SB, Schairer C, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst. 1989;81(24):1879-86.
56. Rosner B, Colditz GA. Nurses' health study: log-incidence mathematical model of breast cancer incidence. J Natl Cancer Inst. 1996;88(6):359-64.
57. Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. Stat Med. 2004;23(7):1111-30.

Appendix Table 1. Examples of Risk Factors for Women Aged 50-74 y Corresponding to the Relative Risk Levels in the Simulation Models

Published Risk Estimates	Risk Group	Comparison Group*	Reference
Relative risk in simulation models: 1.3			
1.12	Age at menopause ≥55 y	Age at menopause 50-54 y	18
1.19	Age at menarche <11 y	Age at menarche 13 y	18
1.21-1.46	≥25 g alcohol per day	No alcoholic beverage consumption	19, 20
1.25-1.28	Use of estrogen plus progestin postmenopausal hormones	Never use of postmenopausal hormones	21-23
1.30-1.52	Nulliparity or age at first full-term pregnancy ≥25 y	Age at first full-term pregnancy <22 y	24
1.42	Body mass index ≥30 kg/m^2 among never-users of postmenopausal hormones	Body mass index <25 kg/m^2 among never-users of postmenopausal hormones	17
1.47-1.99	1 first-degree family member diagnosed with breast cancer	No family members diagnosed with breast cancer	25-27
Relative risk in simulation models: 2.0			
1.44-2.07	History of benign breast disease, not otherwise specified	No history of benign breast disease	27, 28
1.66-2.02	History of proliferative disease without atypia	No history of benign breast disease	27, 28
2.3-3.9	≥2 first-degree family members with breast cancer	No family members diagnosed with breast cancer	25-27
Relative risk in simulation models: 4.0			
3.29-5.84	History of lobular carcinoma in situ	No history of benign breast disease	27, 28
3.36	Highest 1% of polygenic risk score	40th-60th percentile of polygenic risk score	29
3.93	History of atypical hyperplasia, not otherwise specified	No history of benign breast disease	28

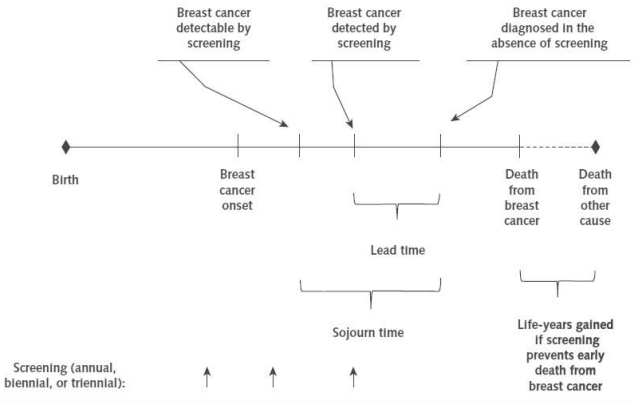
* Risk estimates were based on the comparison group consisting of the largest proportion of women, i.e., "average risk." Women with reduced risk were not modeled, including women who engaged in regular moderate–vigorous physical activity with age at menarche >13 y or age at menopause <50 y with almost entirely fat breast density (Breast Imaging Reporting and Data System category = "a") or who breastfed for ≥1 y. Relative risks associated with breast density categories are shown in Appendix Table 3.

Appendix Table 2. Summary of Model Features*

Feature	Model		
	E	GE	W
Natural history of cancer	Continuous tumor growth	Stage transition	Continuous tumor growth
Tumors obligated to progress	DCIS nonobligate; invasive obligate	DCIS nonobligate; invasive obligate	DCIS and some small invasive are nonobligate; larger invasive obligate
SEER breast cancer data used for model calibration (1975-2010)	Incidence	Incidence	Incidence and mortality
Implementation of screening benefit	Smaller tumor size	Younger age and earlier stage	Younger age and smaller tumor size
Implementation of treatment benefit	Cure fraction based on fatal diameter	Hazard reduction	Cure fraction
Factors affecting treatment benefit	ER and HER2; age; year of and size at diagnosis	ER and HER2; age; year of and stage at diagnosis	ER and HER2; age; year of and stage at diagnosis
Model software program†	Delphi	C++	C++

DCIS = ductal carcinoma in situ; E = Erasmus Medical Center; ER = estrogen receptor; GE = Georgetown University Medical Center and Albert Einstein College of Medicine; HER2 = human epidermal growth factor receptor 2; SEER = Surveillance, Epidemiology, and End Results; W = University of Wisconsin–Madison and Harvard Medical School. * Adapted from reference 14. Additional information is available at https://resources.cisnet.cancer.gov/registry/site-summary/breast. † Combined output from all 3 models was analyzed using SAS software, version 9.4 (SAS Institute).

Appendix Figure. Schema representing breast cancer natural history and screening as simulated in the models.



Sojourn time is the duration of the preclinical, screen-detectable phase of the tumor. Lead time is the interval from screen detection to the time of clinical diagnosis, which is when the tumor would have surfaced without screening. See Appendix Table 2 for the description of the implementation of screening benefit in the 3 simulation models.

Appendix Table 3. Age-Specific Model Input Parameters, by Breast Density and Screening Round for Digital Mammography Performance*

Age, by Breast Density	Density Prevalence	Density Relative Risk†	Screening Frequency	Sensitivity for Invasive Cancer	Sensitivity for DCIS	Specificity	Biopsy After False-Positive Mammogram, ‡
Almost entirely fatty							
50-64 y	0.097	0.50	First	0.948	0.955	0.903	23
			Annual	0.868	0.921	0.948	11
			Biennial	0.921	0.943	0.944	14
			Triennial	0.922	0.921	0.935	15
≥65 y	0.135	0.61	First	0.963	0.955	0.916	23
			Annual	0.903	0.922	0.955	11
			Biennial	0.943	0.944	0.952	14
			Triennial	0.944	0.921	0.944	15
Scattered fibroglandular density							
50-64 y	0.464	0.84	First	0.930	0.949	0.843	23
			Annual	0.826	0.912	0.912	11
			Biennial	0.895	0.937	0.906	14
			Triennial	0.895	0.912	0.892	15
≥65 y	0.533	0.94	First	0.950	0.950	0.863	23
			Annual	0.871	0.913	0.924	11
			Biennial	0.924	0.937	0.919	14
			Triennial	0.924	0.912	0.907	15
Heterogeneously dense							
50-64 y	0.376	1.25	First	0.876	0.965	0.812	23
			Annual	0.716	0.938	0.894	12
			Biennial	0.818	0.956	0.886	14
			Triennial	0.819	0.938	0.870	17
≥65 y	0.300	1.28	First	0.909	0.965	0.836	23
			Annual	0.782	0.938	0.908	12
			Biennial	0.865	0.956	0.901	14
			Triennial	0.865	0.938	0.887	17
Extremely dense							
50-64 y	0.063	1.53	First	0.822	0.944	0.857	23
			Annual	0.623	0.904	0.921	12
			Biennial	0.747	0.930	0.915	14
			Triennial	0.748	0.903	0.903	17
≥65 y	0.032	1.45	First	0.868	0.944	0.876	23
			Annual	0.702	0.904	0.932	12
			Biennial	0.808	0.931	0.927	14
			Triennial	0.809	0.904	0.916	17

DCIS = ductal carcinoma in situ. * Annual mammography was defined as 9- to 18-mo intervals; biennial mammography was defined as 19- to 30-mo intervals; triennial mammography was defined as

31- to 42-mo intervals. Data were obtained from the Breast Cancer Surveillance Consortium. † Age-specific relative risk for breast cancer associated with breast density; reference group is women with average density. ‡ Corrected for missing data.

Appendix Table 4. Median (Range) Lifetime Breast Cancer Outcomes per 1000 Women in the Absence of Screening, by Relative Risk, Breast Density, and Age Group From 3 Simulation Models*

Relative Risk, by Density	Ages 50-74 y†			Ages 65-74 y‡		
	Breast Cancer Deaths	Life-Years§	QALYs§	Breast Cancer Deaths	Life-Years§	QALYs§
Almost entirely fatty						
1.0	11.7 (7.2-14.0)	33.5 (32.1-33.7)	26.5 (25.4-26.7)	8.9 (4.5-9.5)	20.7 (19.3-21.0)	15.8 (14.7-16.0)
1.3	15.0 (9.2-17.8)	33.5 (32.0-33.7)	26.5 (25.4-26.6)	11.3 (5.8-11.9)	20.7 (19.2-21.0)	15.8 (14.7-16.0)
2.0	22.6 (13.7-25.4)	33.4 (31.9-33.6)	26.4 (25.3-26.5)	16.6 (8.5-16.8)	20.7 (19.2-20.9)	15.8 (14.6-15.9)
4.0	41.9 (25.3-42.0)	33.2 (31.6-33.2)	26.2 (25.0-26.2)	25.4 (14.7-30.0)	20.6 (19.1-20.7)	15.7 (14.5-15.8)
Scattered fibroglandular density						
1.0	19.2 (11.7-20.4)	33.4 (32.0-33.6)	26.4 (25.4-26.6)	13.1 (7.3-14.0)	20.7 (19.2-20.9)	15.8 (14.7-15.9)
1.3	24.5 (14.9-25.4)	33.4 (31.9-33.5)	26.4 (25.3-26.5)	16.6 (9.2-17.1)	20.7 (19.2-20.9)	15.8 (14.6-15.9)
2.0	35.2 (21.9-36.1)	33.2 (31.7-33.3)	26.3 (25.1-26.3)	22.8 (12.9-24.2)	20.6 (19.1-20.8)	15.7 (14.6-15.8)
4.0	53.6 (38.6-64.1)	32.8 (31.4-32.9)	25.9 (24.8-26.0)	31.1 (20.7-41.0)	20.5 (19.0-20.6)	15.6 (14.5-15.7)
Heterogeneously dense						
1.0	26.1 (15.7-29.2)	33.3 (31.9-33.5)	26.4 (25.3-26.4)	17.9 (9.0-21.8)	20.7 (19.2-20.8)	15.8 (14.6-15.9)
1.3	31.8 (19.8-36.9)	33.3 (31.8-33.3)	26.3 (25.2-26.3)	21.3 (11.2-27.2)	20.7 (19.1-20.8)	15.7 (14.6-15.8)
2.0	42.8 (28.6-53.1)	33.0 (31.6-33.1)	26.1 (25.0-26.1)	27.2 (15.6-38.2)	20.6 (19.1-20.6)	15.7 (14.5-15.7)
4.0	61.1 (48.5-88.9)	32.4 (31.2-32.7)	25.5 (24.7-25.8)	33.6 (24.0-59.4)	20.4 (19.0-20.5)	15.5 (14.4-15.6)
Extremely dense						
1.0	29.6 (16.9-37.2)	33.3 (31.8-33.3)	26.3 (25.2-26.3)	19.8 (9.5-28.6)	20.7 (19.1-20.8)	15.8 (14.6-15.8)
1.3	35.8 (21.4-46.6)	33.2 (31.7-33.2)	26.2 (25.1-26.3)	23.4 (11.9-35.3)	20.7 (19.1-20.7)	15.7 (14.6-15.7)
2.0	47.3 (30.7-66.0)	32.8 (31.5-33.0)	25.9 (24.9-26.1)	29.2 (16.5-48.4)	20.5 (19.0-20.6)	15.6 (14.5-15.7)
4.0	64.9 (51.5-105.5)	32.1 (31.1-32.6)	25.3 (24.6-25.7)	34.3 (25.1-70.6)	20.2 (18.9-20.5)	15.3 (14.4-15.6)

QALY = quality-adjusted life-year.

* Values are median numbers (range across models).

† Screening was initiated at age 50 y.

‡ Women who were currently age 65 y and have been screened previously biennially from ages 50-64 y.

§ Undiscounted.