Radiation-Induced Breast Cancer Incidence and Mortality From Digital Mammography Screening: A Modeling Study.

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ABSTRACT

Background

Estimates of risk for radiation-induced breast cancer from mammography screening have not considered variation in dose exposure or diagnostic work-up after abnormal screening results.

Objective

To estimate distributions of radiation-induced breast cancer incidence and mortality from digital mammography screening, considering exposure from screening and diagnostic mammography and dose variation across women.

Design

Two simulation-modeling approaches.

Setting

U.S. population.

Patients

Women aged 40-74 years.

Interventions

Annual or biennial digital mammography screening from age 40, 45, or 50 years until age 74 years.

Measurements

Lifetime breast cancer deaths averted (benefits) and radiation-induced breast cancer incidence and mortality (harms) per 100,000 women screened.

Results

Annual screening of 100,000 women aged 40 to 74 years was projected to induce 125 breast cancers (95% confidence interval [CI]=88–178) leading to 16 deaths (95% CI=11–23) relative to 968 breast cancer deaths averted by early detection from screening. Women exposed at the 95th percentile were projected to develop 246 radiation-induced breast cancers leading to 32 deaths per 100,000 women. Women with large breasts requiring extra views for complete breast examination (8% of population) were projected to have higher radiation-induced breast cancer incidence and mortality (266 cancers, 35 deaths per 100,000 women), compared to women with small or average breasts (113

cancers, 15 deaths per 100,000 women). Biennial screening starting at age 50 reduced risk of radiation-induced cancers 5-fold.

Limitations

Life-years lost from radiation-induced breast cancer could not be estimated.

Conclusions

Radiation-induced breast cancer incidence and mortality from digital mammography screening are affected by dose variability from screening, resultant diagnostic work-up, initiation age, and screening frequency. Women with large breasts may have a greater risk for radiation-induced breast cancer.

Funding source

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INTRODUCTION

Exposure to ionizing radiation from repeated mammography examinations may increase breast cancer risk (1, 2). Radiation-induced breast cancer incidence and mortality associated with recommended screening strategies are suggested to be low relative to breast cancer deaths prevented (3-5). However, prior projected population risks were based on exposure from screening only and assumed only four standard views per screen at the mean radiation dose. Evaluations of screening programs should consider full episodes of care including diagnostic work-up prompted by an abnormal screening result (6). False-positive recalls, breast biopsies, and short-interval follow-up examinations are relatively common in the United States and add radiation exposure from diagnostic mammography (7). Some subgroups of women, such as obese women and women with dense breasts, are more likely to have additional evaluations (7-9), which may increase their risk for radiation-induced cancer.

When risk for radiation-induced breast cancer is being evaluated, it may also be important to consider variation in radiation dose from a single examination. Examinations vary in the number of views performed and dose per view; therefore, some women receive more than the mean dose. The American College of Radiology Imaging Network DMIST (Digital Mammographic Imaging Screening Trial) found an average radiation dose to the breast of 1.86 mGy to the breast from a single digital mammography screening view (10), but dose per view varied widely from 0.15 to 13.4 mGy (**Supplemental Content**) and 21% of digital screening examinations used more than four views (10). Radiation dose is strongly correlated with compressed breast thickness; thus, women with large breasts women tend to receive higher doses per view and may require more than four views for complete examination (10, 11). Women with breast augmentation receive implant-displacement views in addition to standard screening views, which doubles their radiation dose (12). Woman may have repeated views because of movement artifacts or improper breast positioning.

We estimated the distribution of cumulative radiation dose and associated breast cancer risk from full screening episodes to identify subgroups of women who may have a greater risk for radiation-induced cancer because they have factors contributing to greater doses per examination or frequent false-positive screening results that lead to additional radiation exposure from subsequent diagnostic work-up. Using population-based data from the Breast Cancer Surveillance Consortium (BCSC) (13), we estimated the probability of a false-positive screening result followed by additional imaging evaluation, short-interval follow-up, or biopsy. We used data from the BCSC, DMIST, and other sources in 2 simulation models to estimate radiation exposure and radiation-induced breast cancer incidence and mortality associated with 8 potential screening strategies

with different starting ages (40, 45, or 50 years) and screening intervals (annual, biennial, or a hybrid strategy).

METHODS

Screening Strategies

We used 2 complementary stochastic modeling approaches to evaluate the following 8 strategies for screening with digital mammography:

1. Annual screening from ages 40-74, 45-74, and 50-74 years.
2. Biennial screening from ages 40-74, 45-74, and 50-74 years.
3. Hybrid strategy of annual screening from ages 40-49 or 45-49 and biennial screening from ages 50-74 years.

We included the hybrid strategies because more frequent screening has been advocated for younger and premenopausal women due to their greater prevalence of dense breasts and more aggressive tumors, resulting in a greater risk for interval cancer, than older women (14-17). Outcomes were breast cancer deaths averted (benefits) and radiation-induced breast cancer incidence and mortality (harms) associated with a lifetime of mammography screening relative to no screening.

Simulation Modeling Approaches

Figure 1 summarizes our approach. We used 2 complementary stochastic modeling approaches to simulate mammography events associated with radiation exposure and outcomes for a population adherent with each of the 8 screening strategies. The first approach used the Microsimulation of Screening Analysis–Fatal Diameter (MISCAN-Fadia) model (18), which is a detailed natural history model of breast cancer. This approach provided estimates of breast cancer incidence and mortality with and without screening to contextualize estimates of radiation-induced breast cancer cases. Although MISCAN-Fadia models the average effects of screening on a population level, it does not model correlation among repeated mammography results in individual women or the specific types of work-up after an abnormal screening result; thus, it cannot be used to estimate the distribution of cumulative radiation exposure from both screening mammography and subsequent diagnostic work-up among women. Therefore, we developed a new simulation model that provides woman-level exposure histories that were not available from the MISCAN-Fadia model. This new model captures exposure heterogeneity by simulating mammography results and subsequent work-up in each woman and allowing for variability in radiation exposure and breast size.

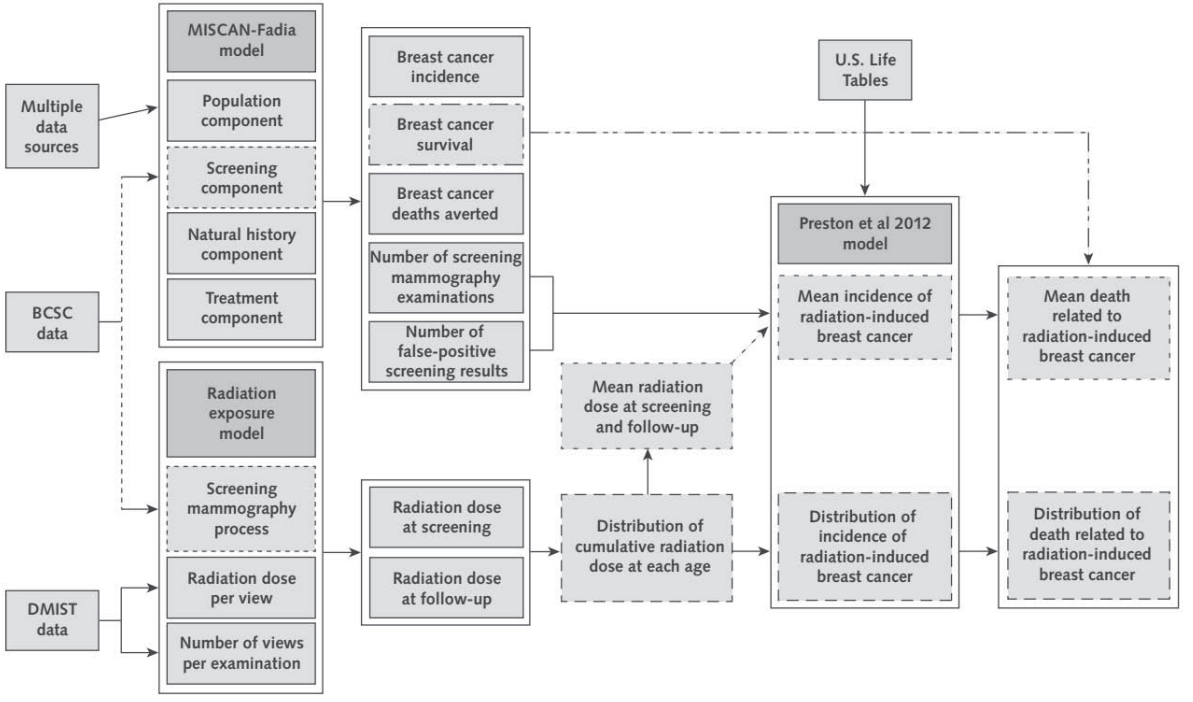

Figure 1 Schematic of 2 modeling approaches used to simulate mammography events and outcomes associated with 8 screening strategies.
Estimates of the number of screening examinations and false-positive results from the MISCAN-Fadia model were combined with the mean radiation dose from the radiation exposure model to estimate mean incidence of radiation-induced breast cancer. Estimates of the probability distribution of cumulative radiation dose at each age among women from the radiation exposure model were used to estimate the probability distribution of radiation-induced breast cancer incidence. Radiation-induced breast cancer incidence was combined with breast cancer survival estimates from the MISCAN-Fadia model to estimate radiation-induced breast cancer mortality. BCSC = Breast Cancer Surveillance Consortium; DMIST = Digital Mammographic Imaging Screening Trial; MISCAN-Fadia = Microsimulation of Screening Analysis–Fatal Diameter.

MISCAN-Fadia Simulation Model

The MISCAN-Fadia microsimulation model simulates individual life histories of women with and without breast cancer in the presence and absence of screening from birth to death from breast cancer or other causes. The model has been described in detail elsewhere (18) and information about the model can be found online (http://cisnet.cancer.gov/); inputs and assumptions are described in our report for the draft USPSTF recommendations (19). In brief, on the basis of BCSC data on sensitivity of digital mammography screening, cancer detection rates, and cancer stage at detection, we estimated thresholds at which tumors become screen-detectable. Screening sensitivity and specificity depended on age, breast density, and screening interval. Breast cancer risk depended on age and breast density. The effect of screening on breast cancer natural history was assessed by modeling continuous tumor growth, in which tumors detected before they reached their fatal diameter were cured and those detected past their fatal diameter led to breast cancer death. We assumed that all women received the mean dose per screening examination and, if recalled, the mean dose associated with diagnostic work-up after a false-positive screening result, both of which were estimated from the radiation exposure model. We also projected breast cancer incidence and mortality with and without screening.

Radiation Exposure Simulation Model

Full details including approach, data sources, and assumptions are available in the **Supplemental Content**. In brief, for each of the 8 screening strategies, we simulated woman-level factors and screening-related events for 100 000 women.

Woman-level factors: Each woman was assigned a compressed breast thickness from the DMIST distribution (**Supplemental Table 2**). Women with a compressed breast thickness of 7.5 cm or greater (8% of DMIST population) were assumed to have large breasts that required extra views for complete examination. On the basis of distributions seen in the BCSC, each woman was assigned a baseline Breast Imaging Reporting and Data System (12) density at the start of screening, which could potentially decrease by 1 category at ages 50 and 65 years (20) (**Supplemental Table 4**).

Evaluation of a positive screening exam: For each screening strategy, we simulated events after a positive screening result that did not lead to a diagnosis of breast cancer (Figure 2) to focus on risk for first breast cancer induced by radiation. We modeled the probability of each event by using data from digital mammography done at BCSC facilities from 2003 to 2011 on women aged 40 to 74 years without a history of breast cancer or cancer diagnosed within 1 year after the examination. At each screening, a woman's probability of recall for additional imaging was based on age, breast density, screening interval, prior screening results, and a woman-specific random effect. If recalled, the probability of referral to biopsy, short-interval follow-up, or return to routine screening was based on age, breast density, and screening interval.

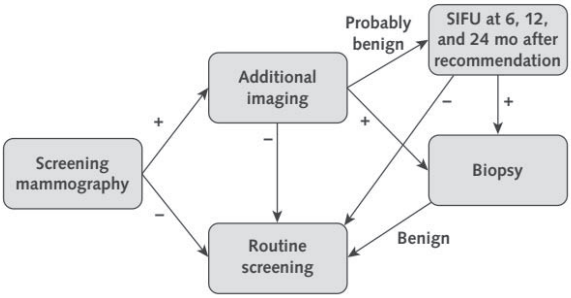

Figure 2 Screening mammography process.
Short-interval follow-up (SIFU) examinations included unilateral diagnostic views on the recalled breast at 6 mo after the initial SIFU recommendation. The examinations included unilateral diagnostic views on the recalled breast plus bilateral routine screening views at 12 and 24 mo after the initial SIFU recommendation for women who received annual screening and 24 mo after the initial SIFU recommendation for those who received biennial screening. The routine screening views could result in recall for additional imaging to work up a new finding, followed by a recommendation for another SIFU examination or tissue biopsy.

Radiation dose: For each screening and diagnostic event, we sampled the number of screening mammography views from the DMIST distribution (**Supplemental Table 1**) and number of views for diagnostic work-up on the basis of expert opinion, conditional on compressed breast thickness (**Supplemental Table 3)**. assumed different distributions of views for women with and without large breasts. We randomly sampled the radiation dose per view on the basis of the DMIST distribution conditional on the woman's compressed breast thickness (**Supplemental figure 1**). For each age, we calculated total breast-level dose by multiplying half the number of views of both breasts by the dose per view. We report the mean and the 5th, 25th, 75th, and 95th percentiles (to quantify exposure leading to increased risk for radiation induced breast cancer) for the number of mammography views and associated dose from each screening examination and all follow-up mammograms within 1 year of a screening examination **Supplemental Table 9**.

Radiation-induced breast cancer incidence and mortality

We estimated radiation-induced breast cancer incidence using the excess absolute risk model from pooled analysis of four cohorts by Preston and colleagues (1), the preferred model for estimating radiation-induced breast cancer incidence (2, 21). Details are provided in the Supplemental Content. Women in these cohorts received cumulative radiation doses of 20 mGy or greater. This level of cumulative radiation exposure is reached after 2 to 4 years of mammography screening and diagnostic work-up (**Supplemental Table 9**). This model assumes that excess risk of radiation-induced breast cancer increases linearly with increasing radiation dose within the exposure ranges from mammography. In addition, risk decreases with increasing age at exposure, especially after

age 50 (a surrogate for menopause) and increases with age, the highest incidence of radiation-induced breast cancer late in life. We modeled the latency period for developing radiation-induced breast cancer using a logistic function that phases in increased breast cancer risk between 4 and 11 years after exposure (21). We estimated radiation-induced breast cancer mortality by multiplying radiation-induced breast cancer incidence by the age-specific case-fatality rates derived from MISCAN-Fadia and assuming 100% adherence to screening and available treatment. We assumed that breast cancers induced by radiation is screen-detected at the same rate as non-induced cancer. We approximated Confidence Intervals (CI) by re-estimating risk using the upper and lower 95% CIs for the risk coefficient, β, because this uncertainty dominates the uncertainty in estimated risk (2, 21).

The MISCAN-Fadia model was programmed in Delphi (Borland). All other analyses were done in R, version 3.1.0 (R Foundation for Statistical Computing) and SAS version 9.4 (SAS Institute).

Role of the Funding Source

This study was funded by the Agency for Healthcare Research and Quality under a contract to support the work of the U.S. Preventive Services Task Force and by the National Cancer Institute. Investigators worked with Task Force members and Agency staff to develop the scope, analytic framework, and key questions. The funding source had no role in model input selection, data synthesis, or data analysis. Agency staff provided project oversight and reviewed the report to ensure that the analysis met methodological standards. The authors are solely responsible for the content and the decision to submit the manuscript for publication.

RESULTS

Radiation exposure

Most radiation exposure from screening and subsequent diagnostic work-up was due to the screening examination (**Supplemental Table 9**). Diagnostic work-up accounted for only 10% of the mean annual radiation dose but 24% of the dose for women with exposure at the 95th percentile. On average, women with large breasts were exposed to 2.3 times more radiation than those with small or average-sized breasts.

Radiation-induced breast cancer incidence and breast cancer death

Risk estimates corresponding to mean exposures were similar for the 2 modeling approaches (Table 1); therefore, we focus on results from the radiation exposure model. We projected that annual screening and diagnostic work-up of 100 000 women aged

Table 1 Comparison of lifetime attributable risks of radiation-induced breast cancer and breast cancer death (per 100,000 women) from two modeling approaches.

Screening Strategy	MISCAN-Fadia Model	Radiation-Exposure Model		
	Mean (95% CI)	Mean (95% CI)	5th percentile (95% CI)	95th percentile (95% CI)
	Lifetime Attributable Risk of Radiation-Induced Breast Cancer (Per 100,000 Women)			
Biennial screening				
Ages 50-74 y	28 (20, 40)	27 (19, 38)	13 (9, 19)	55 (39, 78)
Ages 45-74 y	44 (31, 62)	45 (31, 64)	21 (15, 30)	92 (65, 130)
Ages 40-74 y	67 (47, 96)	68 (48, 97)	33 (23, 47)	138 (97, 196)
Hybrid strategy				
A45-49 y, B50-74 y	57 (40, 81)	59 (41, 84)	29 (20, 41)	118 (82, 168)
A40-49 y, B50-74 y	101 (71, 143)	89 (62, 126)	44 (31, 62)	177 (125, 251)
Annual screening				
Ages 50-74 y	54 (39, 75)	49 (34, 69)	25 (17, 35)	97 (68, 139)
Ages 45-74 y	85 (59, 121)	81 (57, 115)	41 (29, 58)	159 (111, 226)
Ages 40-74 y	129 (90, 183)	125 (88, 178)	64 (44, 90)	246 (171, 349)
Lifetime Attributable Risk of Radiation-Induced Breast Cancer Death (Per 100,000 Women)				
Biennial screening				
Ages 50-74 y	5 (3, 7)	4 (3, 6)	2 (2, 3)	9 (6, 13)
Ages 45-74 y	8 (5, 11)	8 (5, 11)	4 (3, 5)	16 (11, 22)
Ages 40-74 y	12 (8, 17)	12 (8, 17)	6 (4, 8)	24 (17, 34)
Hybrid strategy				
A45-49 y, B50-74 y	10 (7, 14)	10 (7, 14)	5 (3, 7)	20 (14, 29)
A40-49 y, B50-74 y	18 (13, 25)	15 (11, 22)	8 (5, 11)	31 (22, 44)
Annual screening				
Ages 50-74 y	7 (5, 10)	7 (5, 9)	3 (2, 5)	13 (9, 19)
Ages 45-74 y	11 (8, 16)	11 (8, 15)	5 (4, 8)	21 (15, 30)
Ages 40-74 y	16 (12, 23)	16 (11, 23)	8 (6, 12)	32 (22, 45)

40 to 74 years (35 screening examinations per woman) would induce an average of 125 breast cancer cases (95% CI, 88 to 178), resulting in 16 deaths (CI, 11 to 23) (Table 1). Risk projections varied widely, with 100 000 women exposed at the 5th percentile projected to develop 64 radiation-induced cancer cases (CI, 44 to 90), resulting in 8 deaths (CI, 6 to 12), and 100 000 women exposed at the 95th percentile projected to develop 246 radiation-induced cases of cancer (CI, 171 to 349), resulting in 32 deaths (CI, 22 to 45). Women with large breasts requiring extra views for complete examination had more than twice as many cases of radiationinduced breast cancer (mean, 266 cases [CI, 186 to 380]) and breast cancer deaths (mean, 35 deaths [CI, 24 to 50]) than women with small or average-sized breasts (113 breast cancer cases [CI, 79 to 161] and 15 breast cancer deaths [CI, 10 to 21]) (Table 2). Starting screening at age 50 years and following a biennial

Table 2 Mean, 5th percentile, and 95th percentile (95% confidence intervals) of lifetime attributable risks (per 100,000 women) of radiation-induced breast cancer and breast cancer death, by breast size, for different screening strategies.

Screening Strategy	Small or average breasts			Large breasts		
	Mean (95% CI)	5th percentile (95% CI)	95th percentile (95% CI)	Mean (95% CI)	5th percentile (95% CI)	95th percentile (95% CI)
	Lifetime Attributable Risk of Radiation-Induced Breast Cancer (Per 100,000 Women)					
Biennial screening						
Ages 50-74 y	24 (17, 35)	13 (9, 18)	43 (30, 61)	57 (40, 82)	28 (19, 40)	108 (77, 154)
Ages 45-74 y	40 (28, 57)	21 (15, 30)	72 (50, 102)	95 (67, 135)	46 (32, 65)	181 (128, 259)
Ages 40-74 y	61 (43, 87)	33 (23, 46)	107 (76, 152)	144 (100, 205)	71 (49, 101)	266 (188, 384)
Hybrid strategy						
A45-49 y, B50-74 y	53 (37, 75)	29 (20, 41)	91 (64, 130)	125 (87, 178)	60 (43, 88)	233 (162, 335)
A40-49 y, B50-74 y	80 (56, 114)	43 (31, 62)	137 (96, 195)	189 (132, 269)	95 (65, 134)	351 (244, 495)
Annual screening						
Ages 50-74 y	44 (31, 62)	25 (17, 35)	74 (52, 105)	104 (73, 149)	53 (37, 76)	187 (131, 267)
Ages 45-74 y	73 (51, 103)	40 (28, 57)	122 (85, 174)	173 (121, 245)	88 (62, 126)	315 (221, 445)
Ages 40-74 y	113 (79, 161)	63 (44, 89)	189 (133, 268)	266 (186, 380)	136 (95, 193)	487 (339, 700)
Lifetime Attributable Risk of Radiation-Induced Breast Cancer Death (Per 100,000 Women)						
Biennial screening						
Ages 50-74 y	4 (3, 6)	2 (1, 3)	7 (5, 10)	10 (7, 14)	5 (3, 7)	18 (13, 26)
Ages 45-74 y	7 (5, 10)	4 (3, 5)	12 (9, 17)	16 (11, 23)	8 (5, 11)	31 (22, 44)
Ages 40-74 y	11 (7, 15)	6 (4, 8)	19 (13, 26)	25 (17, 35)	12 (8, 17)	46 (33, 67)
Hybrid strategy						
A45-49 y, B50-74 y	9 (6, 13)	5 (3, 7)	16 (11, 22)	21 (15, 31)	10 (7, 15)	40 (28, 57)
A40-49 y, B50-74 y	14 (10, 20)	8 (5, 11)	24 (17, 34)	33 (23, 47)	16 (11, 23)	61 (42, 86)
Annual screening						
Ages 50-74 y	6 (4, 9)	3 (2, 5)	10 (7, 14)	14 (10, 20)	7 (5, 10)	25 (18, 36)
Ages 45-74 y	10 (7, 14)	5 (4, 8)	16 (11, 23)	23 (16, 33)	12 (8, 17)	42 (29, 59)
Ages 40-74 y	15 (10, 21)	8 (6, 12)	25 (17, 35)	35 (24, 50)	18 (12, 25)	63 (44, 91)

strategy (13 screening examinations) greatly reduced risk for radiation-induced breast cancer and breast cancer death (Table 1). Compared with annual screening from age 40 to 74 years, biennial screening from age 50 to 74 years was projected to cause approximately one fifth of the radiation-induced breast cancer cases (mean, 125 cases [CI, 88 to 178] vs. 27 cases [CI, 19 to 38] per 100 000 women, respectively, and 266 cases [CI, 186 to 380] vs. 57 cases [CI, 40 to 82] per 100 000 women with large breasts) (Table 2).

Breast cancer deaths averted per radiation-induced cancer:

From the MISCAN-Fadia model, we projected that 16 947 breast cancer cases would be diagnosed from age 40 years through death per 100 000 women screened annually

Table 2 Mean, 5th percentile, and 95th percentile (95% confidence intervals) of lifetime attributable risks (per 100,000 women) of radiation-induced breast cancer and breast cancer death, by breast size, for different screening strategies.

Screening Strategy	Small or average breasts			Large breasts		
	Mean (95% CI)	5th percentile (95% CI)	95th percentile (95% CI)	Mean (95% CI)	5th percentile (95% CI)	95th percentile (95% CI)
	Lifetime Attributable Risk of Radiation-Induced Breast Cancer (Per 100,000 Women)					
Biennial screening						
Ages 50-74 y	24 (17, 35)	13 (9, 18)	43 (30, 61)	57 (40, 82)	28 (19, 40)	108 (77, 154)
Ages 45-74 y	40 (28, 57)	21 (15, 30)	72 (50, 102)	95 (67, 135)	46 (32, 65)	181 (128, 259)
Ages 40-74 y	61 (43, 87)	33 (23, 46)	107 (76, 152)	144 (100, 205)	71 (49, 101)	266 (188, 384)
Hybrid strategy						
A45-49 y, B50-74 y	53 (37, 75)	29 (20, 41)	91 (64, 130)	125 (87, 178)	60 (43, 88)	233 (162, 335)
A40-49 y, B50-74 y	80 (56, 114)	43 (31, 62)	137 (96, 195)	189 (132, 269)	95 (65, 134)	351 (244, 495)
Annual screening						
Ages 50-74 y	44 (31, 62)	25 (17, 35)	74 (52, 105)	104 (73, 149)	53 (37, 76)	187 (131, 267)
Ages 45-74 y	73 (51, 103)	40 (28, 57)	122 (85, 174)	173 (121, 245)	88 (62, 126)	315 (221, 445)
Ages 40-74 y	113 (79, 161)	63 (44, 89)	189 (133, 268)	266 (186, 380)	136 (95, 193)	487 (339, 700)
Lifetime Attributable Risk of Radiation-Induced Breast Cancer Death (Per 100,000 Women)						
Biennial screening						
Ages 50-74 y	4 (3, 6)	2 (1, 3)	7 (5, 10)	10 (7, 14)	5 (3, 7)	18 (13, 26)
Ages 45-74 y	7 (5, 10)	4 (3, 5)	12 (9, 17)	16 (11, 23)	8 (5, 11)	31 (22, 44)
Ages 40-74 y	11 (7, 15)	6 (4, 8)	19 (13, 26)	25 (17, 35)	12 (8, 17)	46 (33, 67)
Hybrid strategy						
A45-49 y, B50-74 y	9 (6, 13)	5 (3, 7)	16 (11, 22)	21 (15, 31)	10 (7, 15)	40 (28, 57)
A40-49 y, B50-74 y	14 (10, 20)	8 (5, 11)	24 (17, 34)	33 (23, 47)	16 (11, 23)	61 (42, 86)
Annual screening						
Ages 50-74 y	6 (4, 9)	3 (2, 5)	10 (7, 14)	14 (10, 20)	7 (5, 10)	25 (18, 36)
Ages 45-74 y	10 (7, 14)	5 (4, 8)	16 (11, 23)	23 (16, 33)	12 (8, 17)	42 (29, 59)
Ages 40-74 y	15 (10, 21)	8 (6, 12)	25 (17, 35)	35 (24, 50)	18 (12, 25)	63 (44, 91)

CI, confidence interval; y, years; A, annual screening at ages 40-50 or 45-50 and B, biennial screening at 50-74 years.

from age 40 to 74 years (data not shown). The number of breast cancer deaths averted ranged from 627 per 100 000 women screened biennially from age 50 to 74 years to 968 per 100 000 women screened annually from age 40 to 74 years (Table 3). For biennial screening from age 50 to 74 years, we projected a mean of 23 breast cancer deaths averted for each radiation-induced case of breast cancer (CI, 16 to 33) (5th percentile, 48; 95th percentile, 11) and 140 breast cancer deaths averted for each radiation induced breast cancer death (CI, 98 to 199) (5th percentile, 289; 95th percentile, 68). For annual screening from age 40 to 74 years, these ratios were lower, at 8 breast cancer deaths

Table 3 Number of breast cancer deaths averted by screening 100,000 women and ratio of number of breast cancer deaths averted per number (mean, 5th percentile, and 95th percentile) of radiation-induced breast cancers and of radiation-induced breast cancer deaths.

Strategy	Number of breast cancer deaths averted by screening	Overall			Small or average breasts	Large breasts
		Mean (95% CI)	5th Percentile (95% CI)	95th Percentile (95% CI)	Mean (95% CI)	Mean (95% CI)
	Ratio of Breast Cancer Deaths Averted per Radiation-Induced Breast Cancer					
Biennial screening						
Ages 50-74 y	627	23 (16, 33)	48 (34, 69)	11 (8, 16)	26 (18, 37)	11 (8, 16)
Ages 45-74 y	666	15 (10, 21)	31 (22, 45)	7 (5, 10)	17 (12, 24)	7 (5, 10)
Ages 40-74 y	732	11 (8, 15)	22 (16, 32)	5 (4, 8)	12 (8, 17)	5 (4, 7)
Hybrid strategy						
A45-49 y, B50-74 y	717	12 (9, 17)	25 (17, 35)	6 (4, 9)	14 (10, 19)	6 (4, 8)
A40-49 y, B50-74 y	780	9 (6, 13)	18 (12, 25)	4 (3, 6)	10 (7, 14)	4 (3, 6)
Annual screening						
Ages 50-74 y	819	17 (12, 24)	33 (23, 47)	8 (6, 12)	19 (13, 27)	8 (6, 11)
Ages 45-74 y	907	11 (8, 16)	22 (16, 32)	6 (4, 8)	12 (9, 18)	5 (4, 8)
Ages 40-74 y	968	8 (5, 11)	15 (11, 22)	4 (3, 6)	9 (6, 12)	4 (3, 5)
	Ratio of Breast Cancer Deaths Averted per Radiation-Induced Breast Cancer Death					
Biennial screening						
Ages 50-74 y	627	140 (98, 199)	289 (203, 415)	68 (48, 97)	155 (109, 221)	66 (46, 93)
Ages 45-74 y	666	87 (61, 125)	184 (130, 263)	43 (30, 60)	97 (68, 139)	41 (29, 59)
Ages 40-74 y	732	62 (44, 89)	128 (90, 183)	31 (22, 44)	69 (48, 98)	29 (21, 42)
Hybrid strategy						
A45-49 y, B50-74 y	717	71 (50, 102)	145 (102, 207)	35 (25, 51)	79 (56, 113)	33 (23, 48)
A40-49 y, B50-74 y	780	51 (36, 72)	102 (72, 146)	25 (18, 36)	56 (40, 80)	24 (17, 34)
Annual screening						
Ages 50-74 y	819	123 (86, 176)	242 (171, 346)	62 (43, 89)	136 (96, 195)	58 (40, 83)
Ages 45-74 y	907	84 (60, 121)	167 (118, 239)	43 (30, 61)	94 (66, 134)	39 (28, 57)
Ages 40-74 y	968	59 (42, 85)	117 (82, 167)	30 (21, 43)	66 (46, 94)	28 (20, 40)

CI, confidence interval; y, years; A, annual screening at ages 40-50 or 45-50 and B, biennial screening at 50-74 years.

averted per radiation-induced case of breast cancer (CI, 5 to 11) (5th percentile, 15; 95th percentile, 4) and 59 breast cancer deaths averted per radiation-induced breast cancer death among all women (CI, 42 to 85) (5th percentile, 117; 95th percentile, 30). For annual screening from age 40 to 74 years of women with large breasts, ratios were even lower, at 4 breast cancer deaths averted per radiation-induced case of breast cancer (CI, 3 to 5) and 28 per radiation induced breast cancer death (CI, 20 to 40).

DISCUSSION

We improved previous estimates of the potential harms from radiation exposure of screening strategies for breast cancer by using methods that more fully represent the experience of women who have routine digital screening mammography. Our models included radiation exposure from diagnostic evaluations prompted by abnormal screening results and incorporated variation in dose at each screening and diagnostic examination. In addition to the mean, we reported the 5th and 95th percentiles of the population distribution to highlight that some women have risk that is substantially lower or higher than average because of variation in radiation exposure. Most of the increased risk was due to screening examinations with more than 4 views and higher-than-average doses per view. We used DMIST data to model the number of views per screening examination and to incorporate the increased radiation dose per view for thicker compressed breasts. However, even for a given compressed breast thickness, some women received greater doses than others, which was probably due to greater breast density that required more radiation for penetration. Because women with large breasts may require more views per examination and tend to receive a greater dose per view, breast size was an important factor in determining radiation exposure and associated risk. Another reason for greater radiation exposure is false-positive results; additional imaging performed to work up false-positive results accounted for one fourth of the radiation dose received by women at the 95th percentile compared with only one tenth of the radiation dose received by women at the mean.

Relative to a projected 16 947 breast cancer cases diagnosed per 100 000 women aged 40 years or older with annual screening, we estimate that the number of breast cancer cases induced by screening is probably very small, even for women with the greatest radiation exposures. However, relative to the number of breast cancer deaths averted with screening, radiation induced breast cancer incidence is not trivial. Most concerning are numbers projected for annual screening and screening before age 50 years of women with large breasts requiring extra views for complete examination, who have more than twice the risk for radiation induced breast cancer as women with small or average-sized breasts. Although we did not model this explicitly, women with breast augmentation should also have twice the risk for radiation-induced breast cancer because they receive implant-displacement views in addition to standard screening views, resulting in a minimum of 8 views per examination compared with the standard 4 views (12).

The benefit–harm ratio in terms of breast cancer deaths averted per radiation-induced case of breast cancer could be improved by initiating screening at age 50 years instead of 40 years, thereby reducing risk for radiation-induced breast cancer by 60%, or by using biennial screening, which would cut the risk in half compared with annual screening.

Doing both (screening biennially from age 50 to 74 years) would reduce the risk almost 5-fold compared with annual screening from age 40 to 74 years. Several steps should be taken to further improve the benefit–harm ratio. Current efforts to reduce the radiation dose per view should continue. Radiology staff should strive to minimize the number of additional views performed and to reduce false-positive rates, which are much higher in the United States than many other countries, suggesting room for improvement (22-25). Radiation doses from diagnostic mammography could be avoided for certain screen-detected masses amenable to ultrasonography work-up alone. In addition, facilities should ensure that large breasts are imaged using larger detector sizes to minimize the need for extra views for complete examination.

Hendrick (3) also estimated incidence and mortality of radiation-induced breast cancer using DMIST data but used the mean dose for 4 views without accounting for additional radiation exposure from additional screening views received by 21% of women or from diagnostic follow-up imaging. He projected that annual screening of 100 000 women from age 40 to 80 years with an examination-level dose of 3.7 mGy would induce 72 breast cancer cases leading to 20 deaths. For women screened annually from age 40 to 74 years, we estimated fewer breast cancer deaths (16 deaths per 100 000 women), despite more radiation-induced breast cancer cases (125 cases per 100 000 women), because we optimistically assumed 100% adherence to the screening regimen and use of available treatments. In particular, we assumed that 10% to 19% of women diagnosed with breast cancer between ages 40 and 74 years would die of the disease (depending on the screening scenario) compared with recent estimates of more than 23% (26). Thus, we may have underestimated the number of radiation-induced breast cancer deaths. Yaffe and Mainprize (4) projected that screening 100 000 women annually from age 40 to 55 years and biennially thereafter to age 74 years with a dose of 3.7 mGy would induce 86 breast cancer cases and 11 deaths. In comparison, we projected that screening 100 000 women annually from age 40 to 49 years and biennially thereafter to age 74 years would induce 89 breast cancer cases and 15 deaths. Our estimates are probably greater because we accounted for some screening examinations having more than 4 views and for radiation exposure from diagnostic work-up.

Doses from current digital mammography systems may be lower than doses from older DMIST units. Nevertheless, DMIST doses may still be conservative because, similar to most prior studies, dose estimates assumed breast compositions of 50% glandular tissue, which probably underestimates dose by 8% to 18% (27, 28). Although Mammography Quality Standards Act inspections suggest that doses for a digital mammography view decreased 2.5% between 2007 and 2009 (29), these doses were measured with phantoms simulating breasts with a compressed breast thickness at the 30th percentile in DMIST. Radiation dose is highly correlated with compressed breast thickness, which may increase over time with increasing population body mass index (BMI) (30).

The use of digital breast tomosynthesis for screening is increasing in the United States (31). Doses from breast tomosynthesis vary by the strategy; however, the 3-dimensional acquisition results in a radiation dose similar to or slightly greater than standard digital mammography (28, 32, 33). Most U.S. practices offering screening tomosynthesis combine it with digital mammography, which at least doubles doses and the risk for radiation-induced breast cancer. Software approved by the U.S. Food and Drug Administration to generate synthetic 2-dimensional views from tomosynthesis acquisitions will probably eliminate the need for standard digital mammography views and their associated radiation exposure (34); however, the rate at which this software will diffuse into clinical practice is unknown. Estimating radiation-induced cancer risks associated with tomosynthesis screening is further complicated by the expectation that this method will decrease recall rates and potentially eliminate the need for diagnostic mammography to work up some imaging findings (35-41).

Our study had several limitations. We had inadequate information on the percentage of women requiring more than 4 views for complete breast examination. In DMIST, 21% of women required more than 4 screening views (10), although most received only 1 or 2 extra views, probably because of patient movement or poor positioning. On the basis of the observed distribution of compressed breast thickness and number of views, we assumed that 8% of women received extra views because they had large breasts. Of note, the early generation mammography systems used in DMIST had smaller image detectors (10). Most modern units have larger detectors; therefore, the percentage of women requiring extra views because of large breast size is probably less than 8%.

We could not calculate life-years lost due to radiation-induced breast cancer, which may occur later in life than deaths prevented from screening. Because of lack of data, we did not model the association between breast size and the probability of a false-positive result; thus, we may have underestimated exposure from additional work-up in women with large breasts because obese women may be 20% more likely than normal-weight women to have false-positive results (9). We also assumed that the number of breast cancer deaths averted with screening did not vary by breast size; however, screening may prevent more deaths among postmenopausal obese women (who tend to have large breasts) because they have a greater risk for advanced disease (42). In addition, we did not model the association between breast density and radiation dose per view because of lack of representative data. Probabilities for events after screening mammography were based on point estimates from models that used the best available data and did not account for uncertainty due to model misspecification or inherent variability in parameter estimates. We could not estimate 95% CIs for deaths averted with screening because of the computational complexity of the MISCAN-Fadia model and because many input parameters of the model (such as tumor growth rate) are unobservable and

therefore have unknown distributions. We also made several simplifying assumptions (supplementary material).

In conclusion, population projections of radiation induced breast cancer incidence and mortality from mammography screening are affected by variability in doses from screening and resultant diagnostic examinations, age at screening initiation, and screening frequency. Our study suggests that women with large breasts or breast augmentation receive greater radiation doses and may have a greater risk for radiation induced breast cancer and breast cancer death. Radiology practices should strive to ensure that large breasts are imaged with large detectors with the fewest number of views possible.

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Supplemental Table 1 Comparison of lifetime attributable risks of radiation-induced breast cancer and breast cancer death (per 100,000 women) from two modeling approaches

Strategy	MISCAN-Fadia	Radiation Exposure Model
	Mean (95% CI)	Mean (95% CI)
	Lifetime Attributable Risk of Breast Cancer (Per 100,000 Women)	
Biennial screening		
Ages 50-74 y	28 (20, 40)	27 (19, 38)
Ages 45-74 y	44 (31, 62)	45 (31, 64)
Ages 40-74 y	67 (47, 96)	68 (48, 97)
Hybrid strategy		
A45-49 y, B50-74 y	57 (40, 81)	59 (41, 84)
A40-49 y, B50-74 y	101 (71, 143)	89 (62, 126)
Annual screening		
Ages 50-74 y	54 (39, 75)	49 (34, 69)
Ages 45-74 y	85 (59, 121)	81 (57, 115)
Ages 40-74 y	129 (90, 183)	125 (88, 178)
	Lifetime Attributable Risk of Breast Cancer Death (Per 100,000 Women)	
Biennial screening		
Ages 50-74 y	5 (3, 7)	4 (3, 6)
Ages 45-74 y	8 (5, 11)	8 (5, 11)
Ages 40-74 y	12 (8, 17)	12 (8, 17)
Hybrid strategy		
A45-49 y, B50-74 y	10 (7, 14)	10 (7, 14)
A40-49 y, B50-74 y	18 (13, 25)	15 (11, 22)
Annual screening		
Ages 50-74 y	7 (5, 10)	7 (5, 9)
Ages 45-74 y	11 (8, 16)	11 (8, 15)
Ages 40-74 y	16 (12, 23)	16 (11, 23)

CI, confidence interval; y, years; A, annual screening at ages 40-50 or 45-50 and B, biennial screening at 50-74 years.

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Supplement. Supplemental Material

Radiation Exposure Model

For each screening strategy, we simulated screening-related events for 100,000 women from starting age through 74. For each woman, we:

1. Randomly sampled breast density, compressed breast thickness, and a woman-specific random effect for false-positive mammogram probabilities. Determined breast size from compressed breast thickness.

2. Randomly sampled screening results and resulting diagnostic events, conditional on age, breast density, current screening interval, prior screening results, and the woman-specific random effect.

3. Randomly sampled number of views per screening examination and, if recalled, diagnostic events, conditional on breast size, and randomly sampled breast dose per view conditional on compressed breast thickness.

4. Summed the number of mammographic views across events and calculated total dose based on sampled dose per view for each year of age.

5. Estimated radiation-induced breast cancer incidence and mortality through age 100 or death based on total dose at each age.

Data sources

Data were from the Breast Cancer Surveillance Consortium (BCSC) and the American College of Radiology Imaging Network (ACRIN) digital mammographic imaging screening trial (DMIST). The BCSC (13) (http://breastscreening.cancer.gov) has prospectively collected data including patient characteristics and radiology information from community-based facilities since 1994. Characteristics of women are comparable to the US population (43). Breast cancer diagnoses and tumor characteristics are obtained by linking to pathology databases; regional Surveillance, Epidemiology, and End Results (SEER) programs; and state tumor registries.

ACRIN DMIST was powered to compare the screening accuracy of digital and screen-film mammography (44, 45). For this paired trial, 49,528 women provided informed consent to receive both modalities between October 2001 and November 2003. For quality assurance, compressed breast thickness, breast dose, and number of additional views performed were recorded on a subset of examinations at 33 sites. The ACRIN coordinating center provided the distribution for number of views for 5,021 digital examinations and the joint distribution between dose and compressed breast thickness for 19,205 digital mammography views from 4,876 digital examinations.

Breast Size, Compressed Breast Thickness, And Number Of Views Per Examination

We estimated the percentage of women with large breasts based on the number of views and compressed breast thickness observed in DMIST (**Appendix Tables 1 and 3**). Based on expert opinion, we assumed all women with 5 views and a portion of women with 6 views received these extra views due to issues with positioning or movement. In contrast, we assumed a portion of women with 6 views and all women with 7 or more views received extra views because they had large breasts. To estimate the percentage of women with large breasts, we chose a threshold of compressed breast thickness 7.5 cm or larger, consistent with the percentage of women having 6 or more views. This resulted in 8.1% of women having large breasts and 35% of examinations with 6 views being performed in women with large breasts.

DMIST has information only on number of views for screening examinations. For diagnostic examinations and procedure types, we obtained the typical number of views from expert opinion of a radiologist who specializes in breast imaging and scaled the distribution for screening examinations from DMIST based on the typical number of views for that diagnostic exam or procedure type relative to the typical number of screening views. For numbers of rescaled views that were not integers (e.g., 5 views /4 views = 1.3 views), we reassigned women into adjacent groups so the resultant mean number of views was unchanged (e.g., for 1.3 views, we assumed 70% received 1 view and 30% received 2 views). For example, the typical number of screening views is 4 (2 per breast). From DMIST, we estimated that 86% of women without large breasts received 4 views, 9% received 5 views, and 5% received 6 views. Typically, two magnification views are used for an additional evaluation of a positive screening mammogram. Thus, to calculate the distribution of diagnostic views, we halved the number of views from the screening distribution. This resulted in 86% of women receiving 2 views, 9% receiving 2.5 views, and 5% receiving 3 views. We reassigned the 9% of women with 2.5 views to half receiving 2 and half receiving 3. This gave a final distribution for number of magnification views of 91% receiving 2 views and 9% receiving 3 views. Distributions are in **Appendix Table 4**.

Breast density

We assigned a baseline Breast Imaging-Reporting and Data System (BI-RADS) (12) density at the start of screening according to distributions observed in the BCSC (20) (**Appendix Table 2**). At age 50 and 65 years, we allowed breast density to potentially decrease by one category based on transition probabilities that maintain the marginal distributions of density by age (**Appendix Table 2**). We did not account for the inverse relationship between breast density and breast size due to lack of information on the association between event probabilities (i.e., short interval follow-up (SIFU) examinations) and breast size.

Radiation Dose

Radiation dose depends on compressed breast thickness, which depends on breast size. For each woman, we sampled a dose per view based on the distribution observed in DMIST given her compressed breast thickness (**Appendix Figure**). Magnification views have higher radiation dose than standard mammography views (46, 47); however, only part of the breast is typically irradiated (48). Therefore, we assumed the same dose for all views. This assumption is supported by data from Boone, Nosratieh, and Seibert in the 2013 Society for Breast Imaging newsletter (http://www.sbi-online.org/NEWS.aspx). For women with large breasts who receive extra views, most glandular tissue is irradiated on all views; therefore, summing the doses per view for an exam-specific dose for each breast was reasonable (10, 11). We assumed the total bilateral dose per view was half the dose per single breast, as in Law and Faulkner (48). Thus, to calculate the total bilateral dose at each year of age, we summed the total number of views on both breasts from screening and associated diagnostic work-up within the following year, and divided in half.

Events following A Positive Screening exam

Figure 2 in manuscript summarizes possible events following a screening mammogram (12). At each screening mammogram, a woman's probability of recall for additional imaging was based on age, breast density, screening interval, prior screening mammogram results, and a woman-specific random effect. If recalled, the probability of referral to biopsy, short interval follow-up (SIFU), or return to routine screening was based on age, breast density, and screening interval. Following BI-RADS guidelines (12), women recommended for SIFU received diagnostic views at 6, 12, and 24 months after screening mammogram, regardless of screening interval. At each SIFU exam, the probability of a biopsy recommendation was based on age and breast density. Women with a SIFU recommendation also continued to receive bilateral screening views according to their screening schedule with recall and subsequent follow-up recommendations assigned using the probabilities for all BCSC screening exams. A woman assigned to SIFU following recall from screening views restarted the SIFU sequence; otherwise, she continued according to her assigned SIFU schedule. Biopsy type was randomly assigned based on BCSC distributions to be fine needle aspiration, core biopsy, excisional biopsy, or core and excisional biopsy, based on age and breast density. Fine needle aspirations resulted in no additional mammography. For core and excisional biopsies, we randomly assigned ultrasound or stereotactic guidance based on proportions observed in BCSC. Women returned to routine screening following a benign biopsy based on suggestions that 6-month follow-up imaging after biopsy has no benefit (49).

We modeled the probability of events following a screening mammogram using BCSC data. We included digital mammograms of women

aged 40-74 without a history of breast cancer or cancer diagnosed within 1 year after the exam and without breast augmentation. Most analyses included mammograms conducted from 2003 to 2011 with at least one year of complete cancer capture available following the screening exam. Mammograms were classified as screening or SIFU based on the indication given by the radiologist or technologist. For screening mammograms, we excluded unilateral exams and exams performed less than 9 months after a prior mammogram or breast ultrasound exam to avoid misclassifying diagnostic exams as screens. Screening mammograms were classified as annual exams if the previous mammogram was 9–18 months prior and as biennial if 19–30 months prior. We excluded screening mammograms conducted more than 30 months after a prior mammogram because we were interested in estimating events in annual and biennial screeners.

To estimate the recall rates for additional imaging, we included 613,797 digital screening mammograms with sufficient information on prior false-positive results. We defined a recall based on a positive initial BI-RADS assessment (12, 50). We estimated the probability of being recalled for additional views on a screening mammogram using logistic regression including age at exam; BI-RADS breast density; mammogram number (first, second, or third or more); and screening interval for subsequent screens (annual vs. biennial). For second exams, we also included the prior screening result and for third or subsequent exams, we included the prior two screening results. We included a woman-specific random effect to allow for additional correlation of recall across a woman's entire screening regimen and report results for a random effect of 0, corresponding to median rates. Results are in **Supplement Table 1**. To evaluate the model fit, we compared results to prior estimates of cumulative false-positive rates after 10 rounds of screening using a different method (51) and got similar results.

To estimate the probability of events following an abnormal mammogram, we included 725,433 digital mammograms with information on the specific type of recommendation at the end of all imaging work-up. We estimated the probability of recommended follow-up (either return to routine screening, SIFU, or biopsy) after recalled screening mammogram using multinomial logistic regression including age at exam, BI-RADS breast density, and screening interval as predictors. Results are in **Supplement Table 2**.

We estimated the probability of a biopsy recommendation following a SIFU exam using 21,124 SIFU exams. We classified exams as having a biopsy recommendation based on the final BI-RADS assessment and recommendations at the end of all imaging work-up. We fit a logistic regression model including BI-RADS density and age at exam as predictors. Results are in **Supplement Table 3**.

To estimate the distribution for type of biopsy following a positive screening mammogram or SIFU exam, we included 2,284 women with biopsies within 100 days following a positive screening or SIFU conducted in the most recent years available (2010 and 2011), because use of core biopsy instead of excisional biopsy has increased over time. We grouped biopsy events as core biopsy (no excisional, may also include fine

needle aspirations), excisional biopsy (no core biopsy, may also include fine needle aspirations), core and excisional (may also include fine needle aspirations), and fine needle aspiration only. We modeled biopsy type using multinomial logistic regression, including BI-RADS density and age at mammogram as predictors. To estimate the type of biopsy guidance distributions, we selected all biopsies within 100 days of a positive final assessment of a screening or SIFU mammogram. Given inconsistencies in excisional biopsy guidance records, we limited our data to core biopsies only and calculated the proportion of ultrasound and stereotactic biopsies in this sample. Results are in **Supplement Table 4**.

Simplifying Assumptions

Radiation dose depends on the mammography machine used (10), but we could not include this factor in our modeling due to lack of data. Estimates of the U.S. distribution of manufacturers are protected market share information. However, the majority of digital machines used by BCSC facilities are Hologic, which had the highest dose per view but the fewest exams with more than 4 views in DMIST (10). The majority of machines used in DMIST were not Hologic. Thus, if the BCSC is reflective of the U.S., we would likely have underestimated dose for women with small or average breasts but may have overestimated dose for women with large breasts because they would be less likely to need extra views for complete breast examination. We may have slightly underestimated dose due to diagnostic imaging for several reasons. Our estimates of the number of views used for diagnostic evaluations may be conservative, because we assumed that every abnormal screening examination identified only one finding needing diagnostic views and we did not include repeat whole breast views. Also, the chance of repeat images is likely higher for diagnostic spot magnification views for subtle calcifications or masses, and for large-breasted women. In these instances, the technologist may require several images to position small or subtle findings within the field of view. Moreover, magnification spot views require greater exposure time for optimal image resolution, making patient movement more likely.

Radiation-Induced Breast Cancer Incidence And Mortality

The incidence of radiation-induced breast cancer was modeled using the excess absolute risk model from pooled analysis of four cohorts by Preston et al.(1), the preferred model for estimating radiation-induced breast cancers (2, 21). The model formula from page 234 of Preston et al. (1) is

$$\beta D exp(a/50)^{\eta}$$

where β is the risk coefficient per 10,000 person years-Gy, estimated as 10 with 95% confidence interval (CI) 7.0–14.2. D is dose in Gy, e is age at exposure; a is attained age; and η is 3.5 for $a \leq 50$ and 1.0 otherwise. Similar to Berrington et al. (21), we modeled the latency period for

developing radiation-induced breast cancer using a logistic function with shape parameter 0.75, which phases in increased breast cancer risk between 4 and 11 years after exposure. We did not apply a dose and dose-rate effectiveness factor (2) because the Preston 2002 model (1) included data from two cohorts with radiation exposures from high-dose-rate X-rays similar to those used for mammography screening. Also, Preston et al. (1) found no evidence that fractionated exposures result in lower breast cancer risk than acute exposures. We adjusted for competing causes of death using US general population life tables for women (52). Radiation-induced breast cancer mortality was estimated by multiplying radiation-induced breast cancer incidence by the non-radiation induced breast cancer age-specific case-fatality rates derived from MISCAN-Fadia assuming 100% adherence to screening and current treatment. We assumed that breast cancers induced by radiation are screen detected at the same rate as non-induced cancers. Uncertainty ranges were estimated by re-estimating radiation-induced breast cancer risk using the upper and lower 95% CIs for the risk coefficient, β, given this uncertainty dominates the uncertainty in estimated risk (2, 21).

Supplemental Results

From the radiation exposure model simulation results, women who obtained screening annually from ages 40-74 years received an average of 5.0 mammography views (5th percentile=4 views, 95th percentile=9 views) and a dose of 4.8 mGy (5th percentile=2.3 views, 95th percentile=10.7 mGy) from each screening exam and all diagnostic work-up prompted by that screen within a 1-year period (**Appendix Table 5**). The mean dose from screening views was 4.3 mGy (5th percentile=2.2 views, 95th percentile=8.3 mGy), and the mean dose from all diagnostic work-up among women with a false-positive screen was 4.5 mGy (5th percentile=1.7 views, 95th percentile=10.7 mGy). Women with large breasts undergoing annual screening received a mean of 8.4 views (5th percentile=6.0 views, 95th percentile=14.0) and mean dose of 10.0 mGy (5th percentile=4.6 views, 95th percentile=20.8 mGy) from each screening exam plus all diagnostic work-up prompted by that screen, compared to 4.7 views (5th percentile=4 views, 95th percentile=8 views) and 4.3 mGy (5th percentile=2.2 mGy, 95th percentile=8.4 mGy) for women without large breasts.

Supplement Table 1. **Probability of a false-positive recall (median and interquartile range) by age, BI-RADS breast density, screening round, and prior screening results among women aged 40-74 years with digital mammography from 2003-2011 and no cancer diagnosis within 1-year follow-up period, estimated from the Breast Cancer Surveillance Consortium.**

		Screening Schedule = Annual				Screening Schedule = Biennial			
Screening round and prior screening results	**Age, years**	**Almost entirely fat**	**Scattered fibro. densities**	**Hetero. dense**	**Extremely dense**	**Almost entirely fat**	**Scattered fibro. densities**	**Hetero. dense**	**Extremely dense**
		Probability of False-Positive Screening Mammogram, Median (Interquartile Range)							
Round 1	**40-44**	13 (8,20)%	19 (12,29)%	23 (15,35)%	19 (12,28)%	13 (8,20)%	19 (12,29)%	23 (15,35)%	19 (12,28)%
	45-49	18 (11,28)%	27 (18,39)%	32 (21,45)%	26 (17,38)%	18 (11,28)%	27 (18,39)%	32 (21,45)%	26 (17,38)%
	50-54	15 (9,23)%	22 (14,33)%	27 (17,39)%	21 (14,32)%	15 (9,23)%	22 (14,33)%	27 (17,39)%	21 (14,32)%
Round 2									
No prior FP	**40-49**	7 (4,11)%	11 (6,17)%	13 (8,21)%	10 (6,16)%	7 (4,12)%	12 (7,18)%	14 (9,22)%	11 (7,18)%
	50-59	5 (3,9)%	9 (5,14)%	11 (7,17)%	8 (5,14)%	6 (3,10)%	9 (6,15)%	12 (7,19)%	9 (5,15)%
	60-74	5 (3,8)%	8 (5,13)%	10 (6,16)%	7 (4,12)%	5 (3,9)%	8 (5,14)%	10 (6,17)%	8 (5,13)%
Prior FP	**40-49**	6 (4,10)%	10 (6,16)%	12 (7,19)%	9 (6,15)%	7 (4,11)%	11 (6,17)%	13 (8,21)%	10 (6,16)%
	50-59	5 (3,8)%	8 (5,13)%	10 (6,16)%	8 (5,12)%	5 (3,9)%	9 (5,14)%	11 (6,17)%	8 (5,13)%
	60-74	4 (3,7)%	7 (4,11)%	9 (5,14)%	7 (4,11)%	5 (3,8)%	8 (4,12)%	9 (6,15)%	7 (4,12)%
Round 3+									
Past two results TNs	**40-49**	5 (3,8)%	8 (5,13)%	10 (6,16)%	7 (4,12)%	5 (3,9)%	8 (5,14)%	10 (6,17)%	8 (5,13)%
	50-59	4 (2,6)%	6 (4,10)%	8 (5,13)%	6 (3,10)%	4 (2,7)%	7 (4,11)%	8 (5,14)%	6 (4,11)%
	60-74	3 (2,6)%	5 (3,9)%	7 (4,11)%	5 (3,9)%	4 (2,6)%	6 (3,10)%	7 (4,12)%	6 (3,9)%
Past two results TN then FP	**40-49**	6 (4,10)%	10 (6,16)%	12 (7,20)%	9 (6,15)%	7 (4,11)%	11 (6,17)%	13 (8,21)%	10 (6,16)%
	50-59	5 (3,8)%	8 (5,13)%	10 (6,16)%	8 (5,13)%	5 (3,9)%	9 (5,14)%	11 (7,17)%	8 (5,14)%
	60-74	4 (3,7)%	7 (4,12)%	9 (5,14)%	7 (4,11)%	5 (3,8)%	8 (5,13)%	10 (6,16)%	7 (4,12)%
Past two results FP then TN	**40-49**	6 (4,10)%	10 (6,16)%	12 (7,20)%	9 (6,15)%	7 (4,11)%	11 (6,17)%	13 (8,21)%	10 (6,16)%
	50-59	5 (3,8)%	8 (5,13)%	10 (6,16)%	8 (5,13)%	5 (3,9)%	9 (5,14)%	11 (7,17)%	8 (5,13)%
	60-74	4 (3,7)%	7 (4,12)%	9 (5,14)%	7 (4,11)%	5 (3,8)%	8 (5,12)%	10 (6,15)%	7 (4,12)%
Past two results FPs	**40-49**	18 (11,27)%	26 (17,38)%	31 (21,44)%	25 (16,37)%	19 (12,29)%	28 (18,40)%	33 (22,46)%	27 (18,39)%
	50-59	14 (9,23)%	22 (14,33)%	27 (17,39)%	21 (13,32)%	16 (10,24)%	24 (15,35)%	28 (19,41)%	23 (14,34)%
	60-74	13 (8,20)%	20 (12,30)%	24 (15,35)%	19 (12,29)%	14 (8,22)%	21 (13,32)%	26 (17,37)%	20 (13,31)%

BI-RADS = Breast Imaging Reporting and Data Systems; FP, false positive; Fibro = fibroglandular**;** Hetero = heterogeneously
Estimates are based on a mixed effects logistic regression model, and the interquartile range reflects heterogeneity among women based on quartiles of the woman-specific random effect distribution.

Supplement Table 2. **Probability of subsequent events given a false-positive recall, by age and BI-RADS breast density, among women aged 40-74 years with digital mammography from 2003-2011 and no cancer diagnosis within 1-year follow-up period, estimated from the Breast Cancer Surveillance Consortium.**

		Screening Schedule = Annual				Screening Schedule = Biennial			
	Age, years	Almost entirely fat	Scattered fibro. densities	Hetero. dense	Extremely dense	Almost entirely fat	Scattered fibro. densities	Hetero. dense	Extremely dense
Recommendation after false-positive screening mammogram									
Return to normal interval follow-up									
Round 1	**40-44**	52%	56%	55%	50%	52%	56%	55%	50%
	45-49	43%	47%	46%	41%	43%	47%	46%	41%
	50-54	46%	50%	49%	43%	46%	50%	49%	43%
Round 2+	**40-49**	69%	72%	72%	67%	64%	68%	67%	62%
	50-59	66%	70%	69%	64%	61%	65%	64%	58%
	60-74	66%	70%	69%	64%	61%	65%	64%	59%
Short interval follow-up									
Round 1	**40-44**	32%	30%	29%	29%	32%	30%	29%	29%
	45-49	38%	36%	34%	34%	38%	36%	34%	34%
	50-54	29%	28%	26%	26%	29%	28%	26%	26%
Round 2+	**40-49**	20%	19%	18%	19%	23%	21%	20%	21%
	50-59	21%	20%	19%	20%	24%	22%	21%	22%
	60-74	22%	20%	19%	20%	24%	22%	21%	22%
Biopsy									
Round 1	**40-49**	16%	14%	16%	21%	16%	14%	16%	21%
	50-59	19%	17%	20%	25%	19%	17%	20%	25%
	60-74	25%	22%	25%	31%	25%	22%	25%	31%
Round 2+	**40-49**	11%	9%	10%	14%	13%	11%	13%	17%
	50-59	12%	11%	12%	16%	15%	13%	15%	20%
	60-74	12%	10%	12%	16%	15%	13%	15%	19%

BI-RADS = Breast Imaging Reporting and Data Systems; FP = false positive; Fibro = fibroglandular; Hetero = heterogeneously
Due to rounding, some percentages may not add to 100%.

***Supplement Table 3*. Probability of a biopsy at a short-interval follow-up (SIFU) exam among women aged 40-74 years with SIFU exam from 2003-2011 and no cancer diagnosis within 1-year follow-up period, estimated from the Breast Cancer Surveillance Consortium.**

BI-RADS breast density	Age, years	Probability of biopsy at SIFU exam
Almost entirely fat	40-49	2.8%
	50-59	2.9%
	60-74	2.9%
Scattered fibro. densities	40-49	3.3%
	50-59	3.5%
	60-74	3.4%
Heterogeneously dense	40-49	5.0%
	50-59	5.2%
	60-74	5.2%
Extremely dense	40-49	6.2%
	50-59	6.6%
	60-74	6.5%

BI-RADS = Breast Imaging Reporting and Data Systems; SIFU = short interval follow-up; Fibro = fibroglandular

Supplement Table 4. **Distribution of type of biopsy, by BI-RADS breast density and age, among women aged 40-74 years with a biopsy recommendation from a digital mammography examination from 2003-2011 and no cancer diagnosis within 1-year follow-up period, estimated from the Breast Cancer Surveillance Consortium.**

		Type of biopsy (row %)			
BI-RADS Density	**Age, years**	**Core**	**Excisional**	**Core + excisional**	**Fine needle aspiration only**
Almost entirely fat	40-49	71%	3%	3%	23%
	50-59	70%	3%	3%	24%
	60-74	71%	3%	5%	21%
Scattered fibro. densities	40-49	73%	9%	5%	13%
	50-59	74%	7%	5%	14%
	60-74	73%	8%	7%	13%
Heterogeneously dense	40-49	74%	10%	6%	10%
	50-59	75%	8%	6%	11%
	60-74	73%	8%	9%	9%
Extremely dense	40-49	72%	13%	6%	9%
	50-59	73%	11%	6%	9%
	60-74	71%	12%	9%	8%

BI-RADS = Breast Imaging Reporting and Data Systems; Fibro = fibroglandular
Due to rounding, some percentages may not add to 100%.

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PART THREE: Projecting the harms and benefits of risk-based breast cancer screening in the United States