Annals of Internal Medicine ORIGINAL RESEARCH

Radiation-Induced Breast Cancer Incidence and Mortality From Digital Mammography Screening

A Modeling Study

Diana L. Miglioretti, PhD; Jane Lange, PhD; Jeroen J. van den Broek, MSc; Christoph I. Lee, MD, MSHS; Nicolien T. van Ravesteyn, PhD; Dominique Ritley, MPH; Karla Kerlikowske, MD; Joshua J. Fenton, MD, MPH; Joy Melnikow, MD, MPH; Harry J. de Koning, PhD; and Rebecca A. Hubbard, PhD

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 while considering exposure from screening and diagnostic mammography and dose variation among women.

Design: 2 simulation-modeling approaches.

Setting: U.S. population.

Patients: Women aged 40 to 74 years.

Intervention: 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 cancer cases (95% CI, 88 to 178) leading to 16 deaths (CI, 11 to 23), relative to 968 breast cancer deaths averted by early detection from screening. Women exposed at the 95th percentile were projected to develop 246 cases of radiation-induced breast cancer leading to 32 deaths per 100 000 women. Women with large breasts requiring extra views for complete examination (8% of population) were projected to have greater radiation-induced breast cancer risk (266 cancer cases and 35 deaths per 100 000 women) than other women (113 cancer cases and 15 deaths per 100 000 women). Biennial screening starting at age 50 years reduced risk for radiation-induced cancer 5-fold.

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

Conclusion: 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.

Primary Funding Source: Agency for Healthcare Research and Quality, U.S. Preventive Services Task Force, National Cancer Institute.

Ann Intern Med. 2016;164:XXX-XXX. doi:10.7326/M15-1241 **www.annals.org**
For author affiliations, see end of text.
This article was published online first at www.annals.org on 12 January 2016.

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 4 standard views per screening examination 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 those 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 of 1.86 mGy to the breast from a single digital mammography screening view (10), but dose per view varied from 0.15 to 13.4 mGy (**Supplement**, available at www.annals.org), and 21% of digital screening examinations used more than 4 views (10). Radiation dose is strongly correlated with compressed breast thickness; thus, women with large breasts tend to receive greater doses per view and may require more than 4 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). Women

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Context

Repeated digital mammography examinations expose women to ionizing radiation that can increase breast cancer risk.

Contribution

This modeling study found that annual mammography screening of 100 000 women aged 40 to 74 years might induce 125 breast cancer cases and 16 deaths but avert 968 breast cancer deaths because of early detection. Factors associated with increased risk for radiation-induced cancer included large breasts requiring extra views, higher-than-average doses per view, beginning screening at younger ages, and annual screening.

Caution

The model had several assumptions.

Implication

Biennial mammography screening starting at age 50 years and use of the fewest number of views possible would decrease risk for radiation-induced breast cancer.

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: annual screening from age 40 to 74, 45 to 74, or 50 to 74 years; biennial screening from age 40 to 74, 45 to 74, or 50 to 74 years; or a hybrid strategy of annual screening from age 40 to 49 or 45 to 49 years followed by biennial screening from age 50 to 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.

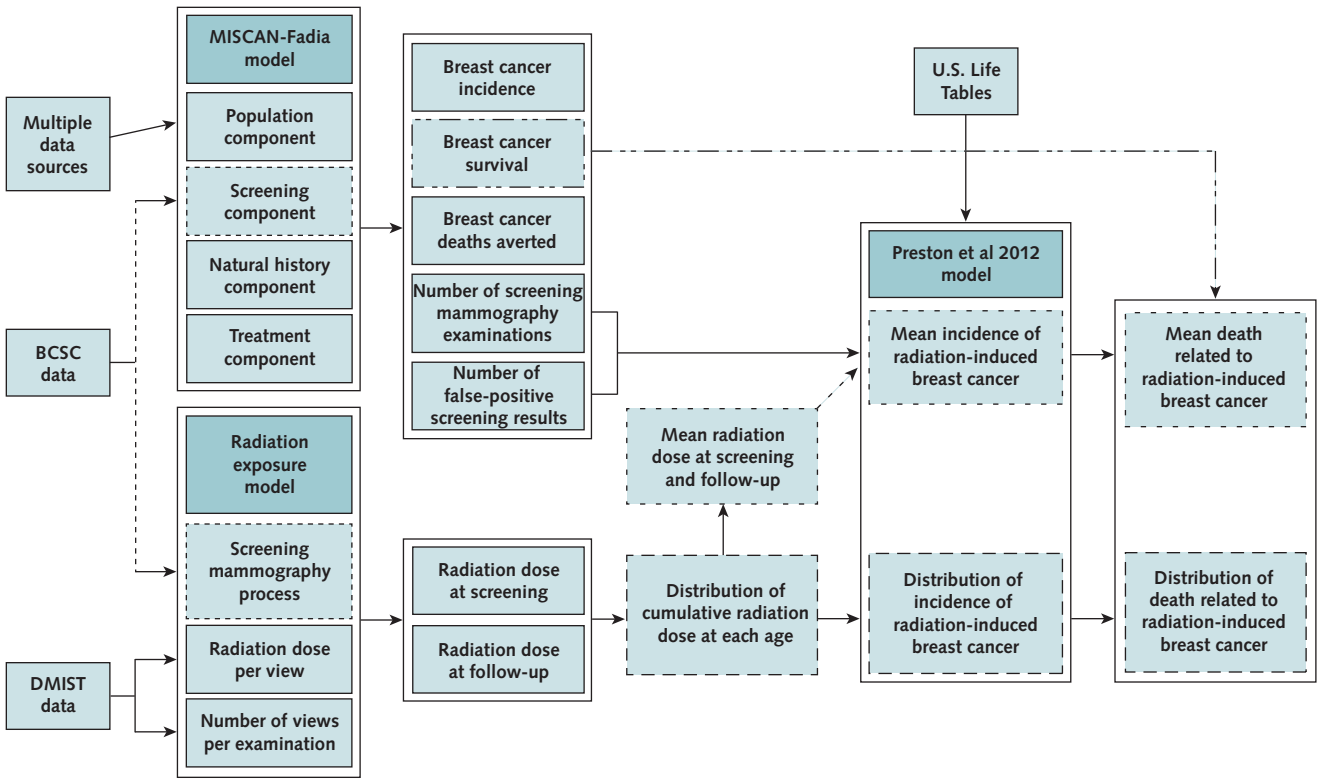
Simulation-Modeling Approaches

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.

MISCAN-Fadia Model

The MISCAN-Fadia 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), information about the model can be found online (http://cisnet.cancer.gov), and inputs and assumptions are described in our report for the draft U.S. Preventive Services Task Force 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

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.

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

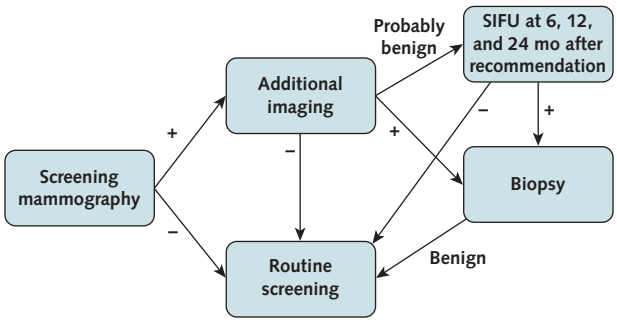
Full details, including approach, data sources, and assumptions, are available in the **Supplement**. In brief, for each of the 8 screening strategies, we simulated woman-level factors and screening-related events for 100 000 women.

Woman-Level Factors. Each woman was assigned a compressed breast thickness from the DMIST distribution (**Appendix Table 1**, available at www.annals.org). 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) (**Appendix Table 2**, available at www.annals.org).

Evaluation of a Positive Screening Result. 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.

Radiation Dose. For each screening and diagnostic event, we sampled the number of screening mammography views from the DMIST distribution (**Appendix Table 3**, available at www.annals.org) and number of views for diagnostic work-up on the basis of expert opinion, conditional on compressed breast thickness (**Appendix Table 4**, available at www.annals.org). We

Figure 2. Screening mammography process.



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. SIFU = short-interval follow-up.

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 (**Appendix Figure**, available at www.annals.org). 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 (**Appendix Table 5**, available at www.annals.org).

Radiation-Induced Breast Cancer Incidence and Mortality

We estimated radiation-induced breast cancer incidence by using the excess absolute risk model from pooled analysis of 4 cohorts by Preston and colleagues (1), the preferred model for estimating radiation-induced breast cancer incidence (2, 21). Details are provided in the **Supplement**. 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 (**Appendix Table 5**). This model assumes that excess risk for 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 years (a surrogate for menopause), and increases with age; the highest incidence of radiation-induced breast cancer occurs late in life. We modeled the latency period for developing radiation-induced breast cancer by 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 of non–radiation-induced breast cancer derived from MISCAN-Fadia and assuming 100% adherence to screening and available treatment. We assumed that breast cancer induced by radiation is screen-detected at the same rate as noninduced cancer. We approximated CIs by reestimating risk for radiation-induced breast cancer by 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 (**Appendix Table 5**). 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 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

Table 1. Comparison of Lifetime Attributable Risks for Radiation-Induced Breast Cancer and Breast Cancer Death From 2 Modeling Approaches*

Screening Strategy	MISCAN-Fadia Model	Radiation Exposure Model		
		Mean	5th Percentile	95th Percentile
Lifetime attributable risk for radiation-induced breast cancer (cases per 100 000 women)				
Biennial screening				
50–74 y	28 (20–40)	27 (19–38)	13 (9–19)	55 (39–78)
45–74 y	44 (31–62)	45 (31–64)	21 (15–30)	92 (65–130)
40–74 y	67 (47–96)	68 (48–97)	33 (23–47)	138 (97–196)
Hybrid strategy				
Annual: 45–49 y; biennial: 50–74 y	57 (40–81)	59 (41–84)	29 (20–41)	118 (82–168)
Annual: 40–49 y; biennial: 50–74 y	101 (71–143)	89 (62–126)	44 (31–62)	177 (125–251)
Annual screening				
50–74 y	54 (39–75)	49 (34–69)	25 (17–35)	97 (68–139)
45–74 y	85 (59–121)	81 (57–115)	41 (29–58)	159 (111–226)
40–74 y	129 (90–183)	125 (88–178)	64 (44–90)	246 (171–349)
Lifetime attributable risk for radiation-induced breast cancer death (deaths per 100 000 women)				
Biennial screening				
50–74 y	5 (3–7)	4 (3–6)	2 (2–3)	9 (6–13)
45–74 y	8 (5–11)	8 (5–11)	4 (3–5)	16 (11–22)
40–74 y	12 (8–17)	12 (8–17)	6 (4–8)	24 (17–34)
Hybrid strategy				
Annual: 45–49 y; biennial: 50–74 y	10 (7–14)	10 (7–14)	5 (3–7)	20 (14–29)
Annual: 40–49 y; biennial: 50–74 y	18 (13–25)	15 (11–22)	8 (5–11)	31 (22–44)
Annual screening				
50–74 y	7 (5–10)	7 (5–9)	3 (2–5)	13 (9–19)
45–74 y	11 (8–16)	11 (8–15)	5 (4–8)	21 (15–30)
40–74 y	16 (12–23)	16 (11–23)	8 (6–12)	32 (22–45)

MISCAN-Fadia = Microsimulation of Screening Analysis–Fatal Diameter.
* Values in parentheses are 95% CIs.

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 radiation-induced 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 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 Case of Breast 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 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 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 incorpo-

Table 2. Lifetime Attributable Risks for Radiation-Induced Breast Cancer and Breast Cancer Death for Different Screening Strategies, by Breast Size*

Screening Strategy	Small or Average-Sized Breasts			Large-Sized Breasts		
	Mean	5th Percentile	95th Percentile	Mean	5th Percentile	95th Percentile
Lifetime attributable risk for radiation-induced breast cancer (cases per 100 000 women)						
Biennial screening						
50–74 y	24 (17–35)	13 (9–18)	43 (30–61)	57 (40–82)	28 (19–40)	108 (77–154)
45–74 y	40 (28–57)	21 (15–30)	72 (50–102)	95 (67–135)	46 (32–65)	181 (128–259)
40–74 y	61 (43–87)	33 (23–46)	107 (76–152)	144 (100–205)	71 (49–101)	266 (188–384)
Hybrid strategy						
Annual: 45–49 y; biennial: 50–74 y	53 (37–75)	29 (20–41)	91 (64–130)	125 (87–178)	60 (43–88)	233 (162–335)
Annual: 40–49 y; biennial: 50–74 y	80 (56–114)	43 (31–62)	137 (96–195)	189 (132–269)	95 (65–134)	351 (244–495)
Annual screening						
50–74 y	44 (31–62)	25 (17–35)	74 (52–105)	104 (73–149)	53 (37–76)	187 (131–267)
45–74 y	73 (51–103)	40 (28–57)	122 (85–174)	173 (121–245)	88 (62–126)	315 (221–445)
40–74 y	113 (79–161)	63 (44–89)	189 (133–268)	266 (186–380)	136 (95–193)	487 (339–700)
Lifetime attributable risk for radiation-induced breast cancer death (deaths per 100 000 women)						
Biennial screening						
50–74 y	4 (3–6)	2 (1–3)	7 (5–10)	10 (7–14)	5 (3–7)	18 (13–26)
45–74 y	7 (5–10)	4 (3–5)	12 (9–17)	16 (11–23)	8 (5–11)	31 (22–44)
40–74 y	11 (7–15)	6 (4–8)	19 (13–26)	25 (17–35)	12 (8–17)	46 (33–67)
Hybrid strategy						
Annual: 45–49 y; biennial: 50–74 y	9 (6–13)	5 (3–7)	16 (11–22)	21 (15–31)	10 (7–15)	40 (28–57)
Annual: 40–49 y; biennial: 50–74 y	14 (10–20)	8 (5–11)	24 (17–34)	33 (23–47)	16 (11–23)	61 (42–86)
Annual screening						
50–74 y	6 (4–9)	3 (2–5)	10 (7–14)	14 (10–20)	7 (5–10)	25 (18–36)
45–74 y	10 (7–14)	5 (4–8)	16 (11–23)	23 (16–33)	12 (8–17)	42 (29–59)
40–74 y	15 (10–21)	8 (6–12)	25 (17–35)	35 (24–50)	18 (12–25)	63 (44–91)

* Values in parentheses are 95% CIs.

rated 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

Table 3. Number of Breast Cancer Deaths Averted by Screening 100 000 Women and Number of Breast Cancer Deaths Averted per Case of and Death From Radiation-Induced Breast Cancer*

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

* Values in parentheses are 95% CIs.

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 doses 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 (30).

The use of digital breast tomosynthesis for screening is increasing in the United States (31). Doses from breast tomosynthesis vary by strategy; however, the

3-dimensional acquisition generally uses 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 (**Supplement**).

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.

From University of California, Davis, School of Medicine, Davis, California; University of California, Davis, Sacramento, California; Group Health Research Institute, University of Washington, and Hutchinson Institute for Cancer Outcomes Research, Fred Hutchinson Cancer Research Center, Seattle, Washington; Erasmus MC University Medical Center Rotterdam, Rotterdam, The Netherlands; University of California, San Francisco, San Francisco, California; and University of Pennsylvania, Philadelphia, Pennsylvania.

Disclaimer: The authors are responsible for study design, analysis and interpretation of the data, writing of the manuscript, and the decision to submit the manuscript for publication. The findings and conclusions in this article are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the funding sources.

Acknowledgment: The authors thank Benjamin Herman, PhD, at the American College of Radiology Imaging Network coordinating center for providing the DMIST data and helping with data interpretation; John Boone, PhD, Professor and Vice Chair of Radiology and Professor of Biomedical Engineering at the University of California, Davis, Medical Center, for helpful input and suggestions on our modeling strategy; Chris Tachibana, PhD, from the Group Health Research Institute for scientific editing; and an anonymous reviewer from the American College of Radiology Imaging Network for his/her comments on an earlier draft.

Grant Support: By the Agency for Healthcare Research and Quality (grant HHSA-290-2012-00015I), U.S. Preventive Services Task Force, and National Cancer Institute (grants P01CA154292, 5U01CA152958, and R03CA182986). Collection of mammography data was supported by the BCSC, which is funded by the National Cancer Institute (grants P01CA154292, HHSN261201100031C, and U54CA163303). The collection of BCSC data was supported in part by several state public health departments and cancer registries throughout the United States. For a full description of these sources, visit http://breastscreening.cancer.gov/work/acknowledgement.html. Primary research and data collection for the American College of Radiology Imaging Network DMIST were supported by the National Cancer Institute (grants U01 CA80098, U01 CA80098-S1, U01 CA79778, and U01 79778-S1).

Disclosures: Dr. Miglioretti reports grants from the Agency for Healthcare Research and Quality and National Cancer Institute during the conduct of the study. Dr. Lee reports grants and personal fees from GE Healthcare outside the submitted work. Dr. van Ravesteyn reports grants from the National Can-

cer Institute, National Institutes of Health, during the conduct of the study. Dr. Melnikow reports other from the Agency for Healthcare Research and Quality during the conduct of the study. Dr. Hubbard reports grants from the National Institutes of Health during the conduct of the study. Authors not named here have disclosed no conflicts of interest. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M15-1241.

Reproducible Research Statement: *Study protocol:* Available from Dr. Miglioretti (e-mail, dmiglioretti@ucdavis.edu). *Statistical code:* The statistical code for the MISCAN-Fadia model is not available. The other statistical code is available from the BCSC's statistical coordinating center (e-mail, SCC@ghc.org). *Data set:* The BCSC data set is available with approval of the BCSC Steering Committee (http://breastscreening.cancer.gov).

Requests for Single Reprints: Diana L. Miglioretti, PhD, Department of Public Health Sciences, University of California, Davis School of Medicine, One Shields Avenue, Medical Science Building 1C, Room 144, Davis, CA 95616; e-mail, dmiglioretti@ucdavis.edu.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Dr. Miglioretti: Department of Public Health Sciences, University of California, Davis School of Medicine, One Shields Avenue, Medical Science Building 1C, Room 144, Davis, CA 95616.
Dr. Lange: Group Health Research Institute, 1730 Minor Avenue, Suite 1600, Seattle, WA 98101.
Mr. van den Broek and Drs. van Ravesteyn and de Koning: Department of Public Health, Erasmus MC University Medical Center Rotterdam, PO Box 2040, 3000 CA Rotterdam, The Netherlands.
Dr. Lee: Department of Radiology, University of Washington School of Medicine, 825 Eastlake Avenue East, G3-200, Seattle, WA 98109.
Ms. Ritley and Drs. Fenton and Melnikow: Center for Healthcare Policy and Research, University of California, Davis, 2103 Stockton Boulevard, Sacramento, CA 95817.
Dr. Kerlikowske: General Internal Medicine Section, San Francisco Veterans Affairs Medical Center, 111A1, 4150 Clement Street, San Francisco, CA 94121.
Dr. Hubbard: Department of Biostatistics & Epidemiology, University of Pennsylvania, 604 Blockley Hall, 423 Guardian Drive, Philadelphia, PA 19104-6021.

Author Contributions: Conception and design: D.L. Miglioretti, H.J. de Koning, R.A. Hubbard.
Analysis and interpretation of the data: D.L. Miglioretti, J.J. van den Broek, C.I. Lee, N.T. van Ravesteyn, K. Kerlikowske, J.J. Fenton, J. Melnikow, H.J. de Koning, R.A. Hubbard.
Drafting of the article: J. Lange, C.I. Lee, D. Ritley, K. Kerlikowske.
Critical revision of the article for important intellectual content: D.L. Miglioretti, J. Lange, J.J. van den Broek, C.I. Lee, N.T. van Ravesteyn, D. Ritley, K. Kerlikowske, J.J. Fenton, J. Melnikow, H.J. de Koning, R.A. Hubbard.
Final approval of the article: D.L. Miglioretti, J. Lange, J.J. van den Broek, C.I. Lee, N.T. van Ravesteyn, D. Ritley, K. Kerlikowske, J.J. Fenton, J. Melnikow, H.J. de Koning, R.A. Hubbard.
Statistical expertise: D.L. Miglioretti, J. Lange, J.J. van den Broek, H.J. de Koning, R.A. Hubbard.
Obtaining of funding: D.L. Miglioretti, K. Kerlikowske, H.J. de Koning, R.A. Hubbard.
Administrative, technical, or logistic support: D. Ritley.
Collection and assembly of data: J. Lange, J.J. van den Broek, C.I. Lee.

Appendix Table 1. Distribution of Compressed Breast Thickness on Digital Mammography From ACRIN DMIST*

Compressed Breast Thickness, *cm*	Frequency	Percentage	Cumulative Frequency	Cumulative Percentage
2.0	407	2.1	407	2.1
2.5	442	2.3	849	4.4
3.0	911	4.7	1760	9.2
3.5	1017	5.3	2777	14.5
4.0	1771	9.2	4548	23.7
4.5	1947	10.1	6495	33.8
5.0	2648	13.8	9143	47.6
5.5	2477	12.9	11 620	60.5
6.0	2552	13.3	14 172	73.8
6.5	2036	10.6	16 208	84.4
7.0	1447	7.5	17 655	91.9
7.5	772	4.0	18 427	95.9
8.0	453	2.4	18 880	98.3
8.5	195	1.0	19 075	99.3
9.0	62	0.3	19 137	99.6
9.5	34	0.2	19 171	99.8
10.0	32	0.2	19 203	100.0
11.0	5	0.0	19 208	100.0
11.5	1	0.0	19 209	100.0

ACRIN DMIST = American College of Radiology Imaging Network Digital Mammographic Imaging Screening Trial.
* Compressed breast thickness ≥7.5 cm is assumed to correspond to large breasts.

Appendix Table 2. Prevalence of BI-RADS Breast Density (by Age) and Probability of Changing Density Category at Age 50 and 65 Years, Estimated From the Breast Cancer Surveillance Consortium*

Variable	BI-RADS Density			
	Almost Entirely Fat	Scattered Fibroglandular Densities	Heterogeneously Dense	Extremely Dense
	Baseline Probabilities			
Age group				
40–49 years	0.051	0.351	0.465	0.133
50–64 years	0.097	0.464	0.376	0.063
65–74 years	0.133	0.529	0.304	0.033
	Probability of Transitioning to a Lower Breast Density Category at Age 50 Years			
Density at ages 40–49 years	Density at ages 50–64 years			
Almost entirely fat	1.000	0.000	0.000	0.000
Scattered fibroglandular densities	0.131	0.869	0.000	0.000
Heterogeneously dense	0.000	0.343	0.657	0.000
Extremely dense	0.000	0.000	0.525	0.475
	Probability of Transitioning to a Lower Breast Density Category at Age 65 Years			
Density at ages 50–64 years	Density at ages 65–74 years			
Almost entirely fat	1.000	0.000	0.000	0.000
Scattered fibroglandular densities	0.077	0.923	0.000	0.000
Heterogeneously dense	0.000	0.269	0.731	0.000
Extremely dense	0.000	0.000	0.471	0.529

BI-RADS = Breast Imaging Reporting and Data Systems.
* Percentages may not sum to 100 due to rounding.

Appendix Table 3. Distribution of the Number of Screening Mammography Views From ACRIN DMIST

Views, *n*	Percentage
4	79.4
5	8.4
6	6.4
7	2.0
8	2.7
9	0.3
10	0.5
11	0.0
12	0.2
13	0.1

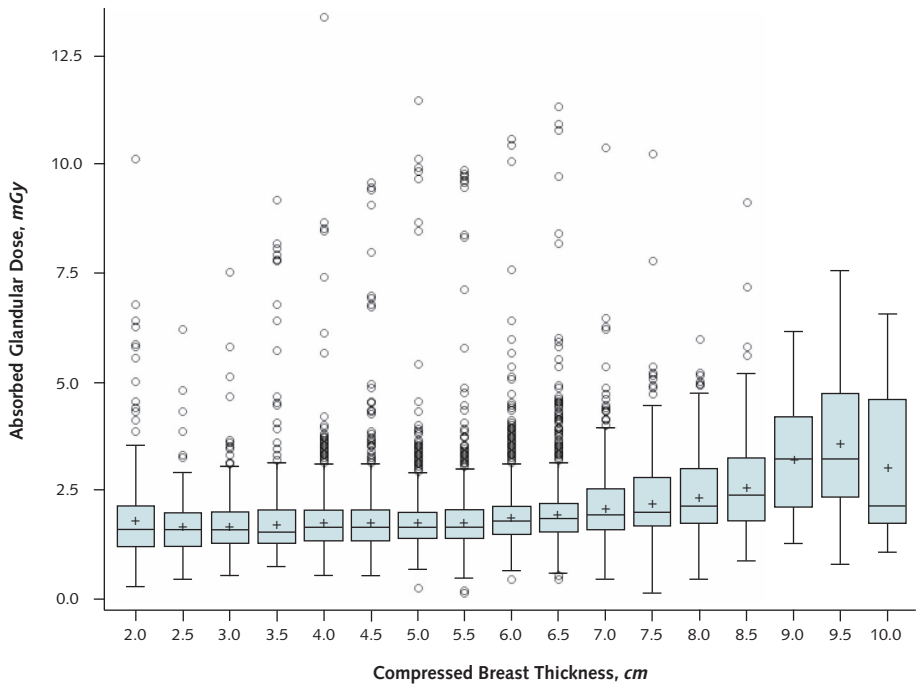
ACRIN DMIST = American College of Radiology Imaging Network Digital Mammographic Imaging Screening Trial.

Appendix Table 4. Number of Plain and Magnification Mammography Views, by Examination or Procedure Type and Breast Size, Estimated From ACRIN DMIST and Expert Opinion, and Percentage of Women With That Number of Views, Where Applicable

Type of Examination	Typical Type and Number of Views Used	Standard Number of Views*	Small or Average-Sized Breasts		Large-Sized Breasts	
			Total Plain Views per Woman (Percentage of Women)	Total Magnification Views per Woman (Percentage of Women)	Total Plain Views per Woman (Percentage of Women)	Total Magnification Views per Woman (Percentage of Women)
Routine screening mammogram†	CC and MLO on both breasts; approximately double or more for large breasts	4	4 (86) 5 (9) 6 (5)	0	6 (28) 7 (25) 8 (33) 9 (4) 10 (6) 11 (1) 12 (2) 13 (1)	0
Diagnostic mammography for additional evaluation‡	ML, spot/magnification CC, and spot/magnification ML on recalled breast; approximately double or more for women with large breasts	3	1 (95) 2 (5)	2 (91) 3 (9)	1 (19) 2 (73) 3 (8)	3 (40) 4 (48) 5 (8) 6 (3) 7 (1)
Ultrasound-guided and other guided biopsy (postbiopsy mammogram only)§	CC, ML on biopsied breast	2	2	0	2	0
Stereotactic (mammography-guided) core biopsy (procedure + postbiopsy mammogram)§	Scout view, two 15-degree orthogonal views, and two orthogonal prefire images on biopsied breast; CC and MLO postmammogram; two scout views for women with large breasts	7	7	0	8	0
Excisional biopsy/wire localization under mammography guidance§	CC scout, CC with wire, MLO, and MLO with wire on biopsied breast	4	4	0	4	0
Excisional biopsy/wire localization under ultrasound guidance§	CC on biopsied breast	1	1	0	1	0
Short-interval follow-up at 6 months for annual and 6 and 12 months for biennial‡	CC, ML, CC magnification, and ML magnification on followed breast; approximately double or more for women with large breasts	4	2 (91) 3 (9)	2 (91) 3 (9)	3 (40) 4 (48) 5 (8) 6 (3) 7 (1)	3 (40) 4 (48) 5 (8) 6 (3) 7 (1)
Short-interval follow-up at 12 and 24 months for annual and 24 months for biennial‡	CC, MLO on both breasts; CC magnification, ML magnification on followed breast; approximately double or more for women with large breasts	6	4 (86) 5 (9) 6 (5)	2 (91) 3 (9)	6 (28) 7 (25) 8 (33) 9 (4) 10 (6) 11 (1) 12 (2) 13 (1)	3 (40) 4 (48) 5 (8) 6 (3) 7 (1)

ACRIN DMIST = American College of Radiology Imaging Network Digital Mammographic Imaging Screening Trial; CC = craniocaudal; ML = mediolateral; MLO = mediolateral oblique.
* Total plain views + magnification.
† DMIST.
‡ Scaled the distribution for screening examinations from DMIST based on the typical number of views for that diagnostic examination or procedure type relative to the typical number of screening views.
§ Expert opinion.

Appendix Figure. Distribution of absorbed glandular (breast) dose of a single screening mammography view, by compressed breast thickness from DMIST.



The boxes show the middle 50% of the data, which is the interquartile range. The horizontal lines within the boxes correspond to the median, and the plus symbols correspond to the mean. The whiskers go out 1.5 box widths or to the last point inside that range. Circles represent values outside the whiskers and are potential outliers. DMIST = Digital Mammographic Imaging Screening Trial.

Appendix Table 5. Distribution of Number of Mammography Views and Radiation Dose From Each Screening Examination and All Follow-up Mammographies and Biopsies Within 1 Year of an Examination for Women Receiving Annual Screening From Age 40 to 74 Years

Variable	Overall	Small or Average-Sized Breasts	Large-Sized Breasts
Number of views from screen and diagnostic work-up			
Mean	5.0	4.7	8.4
5th percentile	4	4	6.0
25th percentile	4	4	7.0
75th percentile	5	5	8
95th percentile	9	8	14
Breast dose (mGy) from screening examination			
Mean	4.3	3.9	9.1
5th percentile	2.2	2.2	4.4
25th percentile	2.9	2.9	6.15
Median	3.7	3.6	8.05
75th percentile	4.8	4.4	11.2
95th percentile	8.3	6.3	17.1
Breast dose (mGy) from diagnostic work-up among women with a false-positive screen			
Mean	4.5	4.1	3.6
5th percentile	1.7	1.7	5.3
25th percentile	2.4	2.4	7.6
Median	3.3	3.2	11.6
75th percentile	5.4	4.9	11.6
95th percentile	10.7	9.3	21.5
Breast dose (mGy) from screening exam and diagnostic work-up among all women			
Mean	4.8	4.3	10.0
5th percentile	2.3	2.2	4.6
25th percentile	3.0	3.0	6.5
Median	3.9	3.8	8.8
75th percentile	5.4	4.9	12.3
95th percentile	10.7	8.4	20.8