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Authors

Kerlikowske, Karla
Zhu, Weiwei
Hubbard, Rebecca A
et al.

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Outcomes of Screening Mammography by Frequency, Breast Density, and Postmenopausal Hormone Therapy

Dr. Karla Kerlikowske, MD, **Ms. Weiwei Zhu, MS**, **Dr. Rebecca A. Hubbard, PhD**, **Dr. Berta Geller, EdD**, **Dr. Kim Dittus, MD**, **Dr. Dejana Braithwaite, PhD**, **Dr. Karen J. Wernli, PhD**, **Dr. Diana L. Miglioretti, PhD**, and **Dr. Ellen S. O'Meara, PhD for the Breast Cancer Surveillance Consortium**

Department of Epidemiology and Biostatistics, University of California, San Francisco (Drs Kerlikowske and Braithwaite); General Internal Medicine Section, San Francisco Veterans Affairs Medical Center, San Francisco (Dr Kerlikowske); Group Health Research Institute, Group Health Cooperative, Seattle, Washington (Ms Zhu and Drs Hubbard, Wernli, Miglioretti, and O'Meara); Department of Biostatistics, University of Washington, Seattle (Dr O'Meara); Departments of Family Medicine and Radiology (Dr Geller) and Department of Medical Oncology (Dr Dittus), College of Medicine, University of Vermont, Burlington; and Department of Public Health Sciences, University of California, Davis, School of Medicine, Davis (Dr Miglioretti)

Abstract

Importance—Controversy exists about the frequency women should undergo screening mammography and whether screening interval should vary according to risk factors beyond age.

Objective—To compare the benefits and harms of screening mammography frequencies according to age, breast density, and postmenopausal hormone therapy (HT) use.

Design—Prospective cohort.

Setting—Data collected January 1994 to December 2008 from mammography facilities in community practice that participate in the Breast Cancer Surveillance Consortium (BCSC) mammography registries.

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Correspondence: Karla Kerlikowske, MD, General Internal Medicine Section, San Francisco Veterans Affairs Medical Center, 4150 Clement St, Mailing Code 111A1, San Francisco, CA 94121 (Karla.Kerlikowske@ucsf.edu).

Group Information: A list of the Breast Cancer Surveillance Consortium (BCSC) investigators and procedures for requesting BCSC data for research purposes are provided at http://breastscreening.cancer.gov.

Conflict of Interest Disclosures: None reported.

Disclaimer: The design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript do not represent those of the National Cancer Institute, and this organization had no role in the final decision to submit the manuscript for publication.

Online-Only Material: The eAppendix is available at http://www.jamainternalmed.com.

Additional Contributions: We thank the participating women, mammography facilities, and radiologists for the data they have provided for this study.

Author Contributions: Dr Kerlikowske had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Kerlikowske, Zhu, Miglioretti, and O'Meara. *Acquisition of data:* Kerlikowske, Zhu, Geller, and Miglioretti. *Analysis and interpretation of data:* Kerlikowske, Zhu, Hubbard, Geller, Dittus, Braithwaite, Wernli, Miglioretti, and O'Meara. *Drafting of the manuscript:* Kerlikowske, Hubbard, Geller, and O'Meara. *Critical revision of the manuscript for important intellectual content:* Kerlikowske, Zhu, Hubbard, Geller, Dittus, Braithwaite, Wernli, Miglioretti, and O'Meara. *Statistical analysis:* Zhu, Hubbard, and Miglioretti. *Obtained funding:* Kerlikowske, Geller, and Miglioretti. *Administrative, technical, and material support:* Kerlikowske and Dittus. *Study supervision:* Miglioretti.

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Participants—Data were collected prospectively on 11 474 women with breast cancer and 922 624 without breast cancer who underwent mammography at facilities that participate in the BCSC.

Main Outcomes and Measures—We used logistic regression to calculate the odds of advanced stage (IIb, III, or IV) and large tumors (>20 mm in diameter) and 10-year cumulative probability of a false-positive mammography result by screening frequency, age, breast density, and HT use. The main predictor was screening mammography interval.

Results—Mammography biennially vs annually for women aged 50 to 74 years does not increase risk of tumors with advanced stage or large size regardless of women's breast density or HT use. Among women aged 40 to 49 years with extremely dense breasts, biennial mammography vs annual is associated with increased risk of advanced-stage cancer (odds ratio [OR], 1.89; 95% CI, 1.06–3.39) and large tumors (OR, 2.39; 95% CI, 1.37–4.18). Cumulative probability of a false-positive mammography result was high among women undergoing annual mammography with extremely dense breasts who were either aged 40 to 49 years (65.5%) or used estrogen plus progestogen (65.8%) and was lower among women aged 50 to 74 years who underwent biennial or triennial mammography with scattered fibroglandular densities (30.7% and 21.9%, respectively) or fatty breasts (17.4% and 12.1%, respectively).

Conclusions and Relevance—Women aged 50 to 74 years, even those with high breast density or HT use, who undergo biennial screening mammography have similar risk of advanced-stage disease and lower cumulative risk of false-positive results than those who undergo annual mammography. When deciding whether to undergo mammography, women aged 40 to 49 years who have extremely dense breasts should be informed that annual mammography may minimize their risk of advanced-stage disease but the cumulative risk of false-positive results is high.

In 2009, the US Preventive Services Task Force issued guidelines that biennial mammography, rather than the previously recommended mammography every 1 to 2 years, be performed for women aged 50 to 74 years.[1] Because of insufficient evidence, the updated guidelines did not consider the influence of breast cancer risk factors beyond age.[2] Women with risk factors that increase the chance of advanced-stage breast cancer at diagnosis may benefit from frequent screening to increase the chance of identifying tumors at an early stage. For example, high breast density is associated with larger tumor size,[3–6] positive lymph nodes,[4,7,8] and advanced-stage disease.[9] Postmenopausal estrogen plus progestogen use for 5 years or more increases the likelihood of development and diagnosis of breast cancer at an advanced stage,[10,11] and risk of advanced stage disease is increased further in women with dense breasts who use postmenopausal hormone therapy (HT).[9]

Few studies have reported on whether risk factors combined with screening mammography frequency influence outcomes. A decision analysis evaluated the benefits and harms of risk-based screening and found that biennial screening of women aged 40 to 49 years with high breast density and with either a first-degree relative with breast cancer or history of breast biopsy had similar benefit-harm ratios as biennial screening of average-risk women in their fifties.[12] Furthermore, women aged 50 to 69 years with low breast density could be screened less often than biennially without decreased benefit.[12]

Our study aimed to extend the literature by reporting whether the benefits (detection of early-stage disease) and harms (false-positive mammography result or biopsy recommendation) differ among women undergoing screening mammography in community practice by screening frequency according to age, breast density, and postmenopausal HT use.

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METHODS

STUDY SETTING AND DATA SOURCES

Data are from the Breast Cancer Surveillance Consortium (BCSC) mammography registries (http://breastscreening.cancer.gov), which are comparable to the US population.[13,14] Registries collected data from community radiology facilities including patient characteristics and clinical information. Radiologists' assessments and recommendations were based on the American College of Radiology's Breast Imaging Reporting and Data System (BI-RADS).[15] Breast cancer diagnoses and tumor characteristics were obtained by linking BCSC data to pathology databases, regional Surveillance, Epidemiology, and End Results (SEER) programs, and state tumor registries, with completeness of reporting estimated at greater than 94.3%.[16] Data were pooled at a central Statistical Coordinating Center. Registries and the Coordinating Center received institutional review board approval for active or passive consenting processes or a waiver of consent to enroll participants, link data, and perform analysis. All procedures were Health Insurance Portability and Accountability Act compliant, and registries and the coordinating center received a federal Certificate of Confidentiality and other protections for the identities of women, physicians, and facilities.

PARTICIPANTS

We evaluated women aged 40 to 74 years with and without breast cancer (Figure 1). Analyses of tumor characteristics included women who were diagnosed as having incident invasive breast cancer or ductal carcinoma in situ, either screen detected or interval cancer, between 1996 and 2008 and who had at least 2 screening mammography examinations before diagnosis. Women were classified based on the time between the 2 most recent screening examinations as either annual (9–18 months apart), biennial (>18–30 months apart), or triennial (>30–42 months apart) (Figure 2). We restricted analyses to breast cancers diagnosed within a specified follow-up period after a woman's index examination (screening mammography before breast cancer diagnosis): within 1 year for annual, 2 years for biennial, and 3 years for triennial screening, as would be done in a randomized trial (Figure 2). To allow adequate follow-up, we included only index examinations that occurred at least 1 year before the end of complete cancer data collection by a woman's BCSC registry for annual interval, at least 2 years for biennial interval, and at least 3 years for triennial interval.

For the cumulative false-positive probabilities analysis, we included first and subsequent screening mammography examinations from 1994 to 2008 from women without a history of breast cancer and without a breast cancer diagnosis within 1 year after mammography. We censored women at their prior screening examination if their self-reported time since last examination differed from that in the database by more than 6 months, to ensure an accurate count of mammography examinations.

MEASURES AND DEFINITIONS

Demographic and breast health history information were obtained on a self-administered questionnaire completed at each mammography examination. We obtained information on history of first-degree relatives (mother, sister, or daughter) with breast cancer and current postmenopausal HT use at the time of mammography. Women aged 50 to 74 years with hysterectomy information were included in analyses by hormone type. Women with a uterus receiving HT were classified as using estrogen plus progestogen (combination HT), whereas women without a uterus receiving HT were classified as using estrogen only, as previously described.[11] We used self-reported race/ethnicity to categorize women as non-Hispanic white, non-Hispanic black, Hispanic, Asian/Native Hawaiian/Pacific Islander, Native

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American/Native Alaskan or other/mixed race. If self-reported race/ethnicity was missing, we used information from cancer registries. Breast density was categorized by radiologists at the time of clinical interpretation using BI-RADS breast density categories: 1=almost entirely fat; 2=scattered fibro-glandular densities; 3=heterogeneously dense; 4=extremely dense.

Breast cancers were classified according to the American Joint Committee on Cancer (AJCC) staging system, sixth edition.[17] We defined advanced-stage disease as AJCC stages IIb, III, or IV and large tumors as greater than 20 mm in diameter. The AJCC sixth edition staging was classified as early- or late-stage disease based on SEER summary stage and other tumor characteristics (see eAppendix; http://www.jamainternalmed.com).

Mammography examinations were considered screening based on the indication reported by radiologists. To minimize misclassifying diagnostic mammography as screening, we excluded examinations that were unilateral or were preceded by a breast imaging study within 9 months.

A false-positive recall or biopsy recommendation was defined as no invasive carcinoma or ductal carcinoma in situ diagnosis within 1 year after a positive screening examination result or before the next screening examination, whichever occurred first. A screening examination was considered positive for recall if the initial BI-RADS assessment was 0 (needs additional imaging evaluation); 4 (suspicious abnormality); 5 (highly suggestive of malignancy); or 3 (probably benign finding with a recommendation for immediate evaluation). A screening examination result was considered positive for biopsy recommendation if the final BI-RADS assessment after all imaging workup and within 90 days after the screening examination was 4 or 5—or was 0 or 3 with a recommendation for biopsy, fine needle aspiration, or surgical consultation. Examinations were excluded from the biopsy recommendation analysis if the final assessment, 90 days after the screening mammography, was BI-RADS 0, with a recommendation for additional imaging, non-specified workup, or missing a recommendation.

STATISTICAL ANALYSIS

We describe the distribution of risk factors among women with and without breast cancer. Among cancer cases, we estimated the proportion with invasive cancer vs ductal carcinoma in situ. Among women with invasive cancer, we estimated distributions of tumor characteristics (stage, size, and lymph node status) at diagnosis by age, screening interval, breast density, and HT use at the study closest to cancer diagnosis. We used logistic regression to estimate odds ratios (ORs) and 95% confidence intervals of adverse (vs more favorable) invasive tumor characteristics associated with screening intervals by breast density, HT use, and age group. Models were adjusted for age in years, BCSC mammography registry, and race/ethnicity. Because breast cancer among women aged 40 to 49 years with fatty breasts is uncommon (<1%), we combined women aged 40 to 49 years with fatty breasts and those with scattered fibroglandular densities.[18] Similarly, breast cancer among women aged 50 to 74 years with extremely dense breasts is uncommon (2%–6%), so we combined women aged 50 to 74 years with heterogeneously and extremely dense breasts.[18]

We estimated the probability of a false-positive first mammography result using logistic regression including breast density and screening interval terms in the model and adjusted for BCSC registry. Probability estimates were standardized to the BCSC mammography registry distribution using indirect (marginal) standardization. We modeled the cumulative probability of false-positive results after 10 years of subsequent screening using previously developed methods.[19] Briefly, we fit logistic regression models for false-positive results at

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each subsequent screening round conditional on screening round number, total number of screening rounds before censoring, screening interval, breast density, and BCSC mammography registry. All estimates were stratified by age (40–49 vs 50–74 years) and by type of HT use for women aged 50 to 74 years. We combined estimates of the false-positive risk at each subsequent screening round according to age at first examination and HT use at each examination to obtain woman-level cumulative false-positive probabilities after 10 years of repeated screening. We report fitted values from this model by breast density, screening interval, age, and HT use.

Analyses of tumor characteristics were performed using SAS version 9.2 statistical software (SAS Institute Inc). Analyses of cumulative false-positive probabilities were performed using R 2.10.1 (R Foundation for Statistical Computing).

RESULTS

RISK OF ADVERSE TUMOR CHARACTERISTICS BY SCREENING FREQUENCY

We included 11 474 women with breast cancer; the majority were 50 years or older and white and had heterogeneously dense or extremely dense breasts. Percentages of interval cancers increased with increasing screening interval (Table 1).

The proportion of tumors associated with less-favorable prognostic characteristics (stage IIb or higher, size >20 mm, and positive lymph nodes) was higher among women with high breast density (heterogeneously dense or extremely dense) compared with women with low or average breast density (fatty or scattered fibroglandular densities) (Table 2). Within density categories, the proportion with less favorable prognostic tumor characteristics did not vary by screening interval except among women with extremely dense breasts, for whom a 3-year screening interval was associated with a higher proportion of advanced stage, large tumors, and positive lymph nodes (Table 2).

We calculated ORs comparing the risk of less favorable tumor characteristics by screening interval (Table 3). Compared with annual mammography, women aged 50 to 74 years undergoing biennial mammography were not at increased risk of less favorable tumor characteristics regardless of breast density or HT use. Women undergoing biennial mammography receiving combination HT with heterogeneously dense or extremely dense breasts had a non–statistically significant increased risk of advanced stage (OR, 1.56; 95% CI, 0.88–2.80) and large tumor size (OR, 1.59; 95% CI, 0.97–2.61). No differences were observed in tumor characteristics among women aged 50 to 74 years undergoing triennial vs biennial mammography. In contrast, women aged 40 to 49 years with extremely dense breasts undergoing biennial compared with annual mammography were at increased risk of advanced stage (OR, 1.89; 95% CI, 1.06–3.39) and large tumor size (OR, 2.39; 95% CI, 1.37–4.18).

In a sensitivity analysis, model results were similar with adjustment for family history of breast cancer. We did not include this factor in the main model because missing values reduced our sample size.

CUMULATIVE PROBABILITY OF FALSE-POSITIVE MAMMOGRAPHY RESULT AND BIOPSY RECOMMENDATION

We included 922 624 women who underwent 2 099 648 screening examinations; more than half of women with extremely dense breasts were aged 40 to 49 years (Table 4).

When screening women aged 50 to 74 years with scattered fibroglandular densities not receiving HT, the cumulative probability of a woman receiving at least 1 false-positive

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mammography result after 10 years was 49.8% with annual, 30.7% with biennial, and 21.9% with triennial screening (Table 5). Estimates were similar among estrogen-only users. Among women aged 50 to 74 years undergoing annual mammography, estimates were highest among women with extremely dense (65.8%) or heterogeneously dense breasts (68.1%) receiving combination HT. Estimates were lowest for women aged 50 to 74 years with fatty breasts (30.3% with annual, 17.4% with biennial, and 12.1% with triennial mammography not receiving HT), and even low among HT users. The cumulative probability of at least 1 false-positive mammography result after 10 years was highest among women aged 40 to 49 years undergoing annual screening with heterogeneously dense (68.9%) or extremely dense breasts (65.5%). Estimates of the cumulative probability of a woman receiving at least 1 false-positive biopsy recommendation after 10 years had a similar pattern to that of false-positive mammography results: (1) risk decreased as screening interval increased, (2) risk was lowest among women with fatty breasts, and (3) risk was highest among combination HT users with dense breasts (Table 5).

COMMENT

We found that biennial screening mammography for most women aged 40 to 49 and 50 to 74 years, even among those with high breast density or receiving combination HT, results in a similar risk of presenting with advanced-stage disease as annual screening mammography. Notably, most women who undergo annual mammography are at high risk of false-positive mammography results and biopsy recommendations without added benefit from more frequent screening. However, a small proportion of women aged 40 to 49 years with extremely dense breasts are more likely to present with advanced-stage disease if they undergo biennial vs annual screening mammography. This benefit is counterbalanced by a higher risk of cumulative false-positive mammography results with annual screening.

Our results are consistent with those of randomized controlled trials, a population-based screening program, a community-based study, and statistical models that report annual mammography has minimal if any additional benefit over biennial mammography for women aged 50 to 74 years.[12,20–24] For women aged 40 to 49 years, less data are available on effectiveness by screening interval. Of 6 statistical models that incorporate US population-based breast cancer incidence and mortality information from the SEER program and US population-based mammography outcomes from the BCSC, 4 showed no additional deaths averted by annual vs biennial screening for women aged 40 to 49 years.[23] A recent BCSC community-based study found no statistically significant absolute difference in the overall proportion of advanced-stage cancer with biennial compared with annual screening.[24] We add to the literature by showing that for women aged 40 to 49 years with extremely dense breasts, who have increased risk of advanced-stage disease[9] and missed breast cancers by mammography,[25,26] annual screening has added benefit to detect breast cancer at an earlier stage than biennial screening. As others have shown,[12,23,27] we found the added benefit of annual screening is offset by increased risk of false-positive mammography results and breast biopsy recommendations. The 12% to 15% of women aged 40 to 49 years with extremely dense breasts,[18] whose risk of breast cancer is similar to average-risk women aged 50 to 59 years,[12,27,28] will need to decide if the added benefit is outweighed by the additional harms of annual screening including doubling the number of mammograms and increased risk of false-positive mammography results and breast biopsy recommendations. For the majority of women aged 40 to 49 years without extremely dense breasts, biennial mammography is associated with a similar risk of advanced-stage disease as annual screening, and the cumulative risk of false-positive screening results and biopsy recommendations is lower.

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Although postmenopausal combination HT use for 5 years or more increases the likelihood of developing breast cancer that is diagnosed at an advanced stage,[9–11] and this risk is increased even more in women with dense breasts,[9] the risk of advanced disease did not differ significantly in HT users with dense breasts undergoing biennial vs annual mammography. Perhaps frequent screening does not decrease the risk of advanced-stage disease in women with dense breasts receiving combination HT because increased breast density obscures identification of tumors and/or tumors grow rapidly in a short period.[29–31] Alternatively, we may have had insufficient statistical power to observe a benefit from annual mammography. Our results need confirmation to determine whether biennial mammography increases the risk of advanced disease in women with extremely dense breasts receiving combination HT.

Prior studies report that postmenopausal combination HT increases the risk of abnormal mammogra-phy.[10,26] We found that for women aged 50 to 74 years with average or high breast density, receiving combination HT increases the cumulative probability of receiving at least 1 false-positive mammography result after 10 years, and the magnitude of the risk is similar to that of women aged 40 to 49 years with high breast density. Women receiving combination HT should be informed of the increased risk of false-positive mammography results compared with women their age not receiving HT and that stopping HT can reduce this risk.[32,33]

Women with fatty breasts are at low risk of breast cancer, regardless of age, menopausal status, family history of breast cancer, history of breast biopsy, and HT use.[9,34] Moreover, women with fatty breasts are at reduced risk of advanced-stage disease.[9] Our results show that women with fatty breast density have the lowest cumulative probability of false-positive mammography results or biopsy recommendations after 10 years of screening. This low probability is probably because radiologists can easily discern whether a lesion is suggestive of malignancy in women with fatty breasts because the characteristics of the lesion are not obscured by normal fibroglandular tissue, so fewer women are recalled for diagnostic evaluation. Taken together, our results suggest there is no added benefit of screening women with fatty breasts annually and false-positive results are low compared with women with high breast density. One study supporting our findings found that mammography every 3 to 4 years was cost-effective for women aged 50 to 79 years with fatty breasts and no other risk factors.[12]

In observational studies, women at high breast cancer risk may undergo more frequent screening than low-risk women, which could spuriously inflate advanced disease rates among frequent screening. To minimize this potential bias, we evaluated the proportion of cases with advanced disease. Although more than 10 000 breast cancers were identified among women undergoing screening mammography, we had limited statistical power to examine subgroups of women with fatty breasts and those undergoing triennial mammography. Misclassification of BI-RADS density because of modest interrater agreement between radiologists[35–37] could result in under or overestimation of associations with breast cancer outcomes by density category. We evaluated numerous comparisons; some may be significant by chance. Thus, it is important to consider the magnitude of differences and confidence interval widths. Also, most study examinations were film screen. The sensitivity of digital mammography is higher in women with extremely dense breasts,[38] which could result in a smaller difference in tumor outcomes between annual, and biennial screening than we observed. We did not adjust for body mass index because data were missing in 50% of women, mostly because facilities do not collect this information.

In conclusion, women aged 50 to 74 years, regardless of breast density or HT use, can undergo biennial rather than annual mammography because biennial screening does not

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increase the risk of presenting with advanced disease but does substantially reduce the cumulative risk of a false-positive mammography result and biopsy recommendation. Women aged 40 to 49 years with extremely dense breasts who choose to undergo mammography should consider annual screening to decrease the risk of advanced-stage disease but should be informed that annual screening leads to a high cumulative probability of a false-positive mammography result because of the additional screening examinations.

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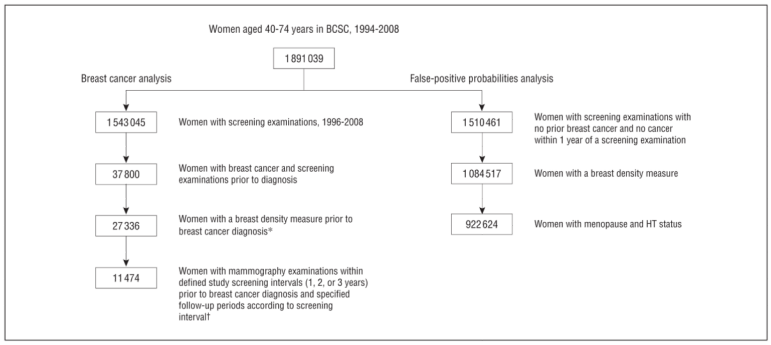

Figure 1.

Study populations. BCSC indicates Breast Cancer Surveillance Consortium; and HT, hormone therapy. *Breast density reported by a subset of mammography facilities. †Of 15862 excluded, 24% have only 1 mammogram prior to cancer diagnosis and 76% are not in defined screening intervals.

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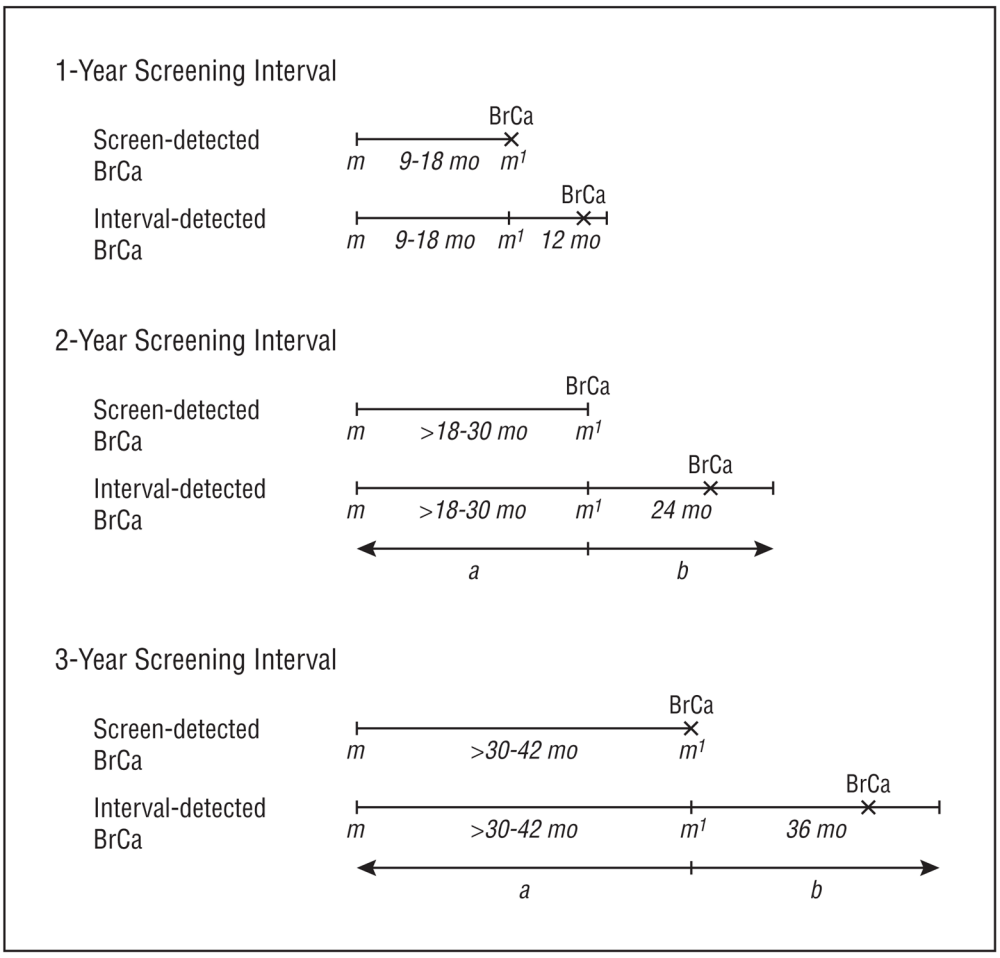

Figure 2.

Overview of study design. Longer vs shorter screening interval may lead to advanced disease detected at the index examination (m^1) owing to longer time for tumor growth since the previous screen (m), or advanced disease is detected clinically after m^1 owing to the longer interval until the next screen. BrCa indicates breast cancer; a, screening interval; b, follow-up period for cancer ascertainment.

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Table 1

Population Characteristics by Screening Interval for Women With Breast Cancer Who Underwent Screening Mammography Between 1996 and 2008

	Screening Interval		
Characteristic	**1 y[a]**	**2 y[b]**	**3 y[c]**
Total No. of women with breast cancer	7039	3476	959
Screening interval time, median, mo	13	24	35
Age, %			
40–49 y	16.7	22.8	29.6
50–59 y	36.7	34.0	34.8
60–69 y	32.4	27.7	24.6
70–74 y	14.1	15.4	10.9
Breast density, %			
Almost entirely fat	3.5	3.7	4.9
Scattered fibroglandular densities	39.9	38.2	39.5
Heterogeneously dense	47.5	47.6	46.4
Extremely dense	9.1	10.5	9.2
Race/ethnicity, %			
White, Non-Hispanic	86.4	82.9	81.3
Black, Non-Hispanic	4.9	6.0	7.6
Hispanic	4.5	5.3	7.1
Asian/Pacific Islander	2.2	3.6	2.4
American Indian/Alaska Native	0.4	0.9	0.1
Other, includes mixed	1.5	1.2	1.4
BMI, %			
Underweight, <18.5	1.3	1.3	1.2
Normal, 18.5–24.9	44.8	40.2	42.9
Overweight, 25.0–29.9	32.0	30.5	30.5
Obese I, 30.0–34.9	14.0	16.5	15.4
Obese II/III, ≥35	7.9	11.4	10.0
First-degree family history of breast cancer, %			
No	76.8	80.2	82.6
Yes	23.2	19.8	17.4
Current hormone therapy use, %			
No	64.0	67.0	73.9
Yes	36.0	33.0	26.1
Estrogen[d]	48.5	45.0	43.3
Combination[e]	51.6	55.0	56.7
Type of detection, %[f]			
Screen detected Interval cancer, mo	70.0	59.4	55.7
0–12	30.0	18.1	15.5
13–24		22.5	16.6

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Characteristic	Screening Interval		
	1 y[a]	2 y[b]	3 y[c]
25–36			12.2

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a]Cancer diagnosed within 12 months of screening examination.

[b]Cancer diagnosed within 24 months of screening examination.

[c]Cancer diagnosed within 36 months of screening examination.

[d]Total of 982 breast cancers.

[e]Total of 1112 breast cancers; combination defined as estrogen plus progestogen.

[f]Screen-detected breast cancer diagnosed after a positive screening mammography result and interval breast cancer detected after a negative screening mammography result and before the next screening examination.

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Table 2

Distribution of Tumor Characteristics by Breast Density and Screening Interval

	Breast Density											
	Fatty			Scattered Fibroglandular Densities			Heterogeneously Dense			Extremely Dense		
	Screening Interval			Screening Interval			Screening Interval			Screening Interval		
Tumor Characteristic	**1 y**	**2 y**	**3 y**	**1 y**	**2 y**	**3 y**	**1 y**	**2 y**	**3 y**	**1 y**	**2 y**	**3 y**
No. of breast cancers (N = 11 474)	244	128	47	2809	1328	379	3346	1654	445	640	366	88
DCIS, % (n=2403)	23.0	19.5	6.4	21.3	19.0	16.1	22.1	19.8	18.9	22.8	25.1	21.6
Invasive, % (n = 9071)	77.0	80.5	93.6	78.7	81.0	83.9	77.9	80.2	81.1	77.2	74.9	78.4
Stage												
No. of invasive cancers	177	88	40	1985	999	291	2382	1248	324	462	268	65
Stage I, %	69.5	60.2	67.5	65.5	63.1	59.8	58.9	56.2	52.5	50.4	48.9	43.1
Stage IIa, %	15.3	25.0	17.5	18.8	22.0	27.5	21.8	22.1	26.9	24.9	25.0	24.6
Stage IIb, %	5.6	8.0	0	6.6	7.1	5.5	9.3	9.5	7.7	13.4	10.1	15.4
Stage III or IV, %	9.6	6.8	15.0	9.0	7.8	7.2	10.0	12.3	13.0	11.3	16.0	16.9
Combined stages[a]												
No. of invasive cancers	180	98	42	2106	1045	307	2507	1283	346	480	272	67
Early, %	84.9	86.7	85.7	85.0	85.7	87.9	81.5	78.8	80.3	75.8	73.9	68.7
Advanced, %	15.0	13.3	14.3	15.0	14.3	12.1	18.5	21.2	19.7	24.2	26.1	31.3
Tumor size												
No. of invasive cancers	175	92	41	2041	1025	298	2468	1261	347	468	263	65
<10 mm, %	41.7	30.4	41.5	32.1	29.2	25.2	25.1	23.6	21.3	21.6	20.5	16.9
10 to <15 mm, %	24.0	27.2	26.8	25.6	24.8	24.5	25.4	22.6	16.4	21.2	18.3	13.8
15–20 mm, %	17.2	18.5	17.1	20.7	23.4	23.1	22.9	25.1	30.0	24.5	21.2	26.2
>20 mm, %	17.1	23.9	14.6	21.5	22.6	27.2	26.6	28.7	32.3	32.7	39.9	43.1
Lymph node												
No. of invasive cancers	181	98	42	2124	1047	309	2526	1291	348	480	271	68
Positive, %	22.7	23.5	16.7	23.6	25.1	22.7	27.6	30.6	32.8	32.7	32.1	42.6
Negative, %	77.3	76.5	83.3	76.4	74.9	77.3	72.4	69.4	67.2	67.3	67.9	57.4

Abbreviation: DCIS, ductal carcinoma in situ.

[a]Combines invasive cancers classified by American Joint Committee on Cancer stage (95.2% of cancers) and Surveillance, Epidemiology, and End Results summary stage (4.8% of cancers).

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Table 3

Odds Ratios of Adverse Invasive Cancer Characteristics by Age, Breast Density Group, and Screening Interval, Adjusted for Age, Breast Cancer Surveillance Consortium Registry, and Race/Ethnicity

	Breast Density and Screening Interval								
	Fatty and Scattered Fibroglandular Densities			Heterogeneously Dense			Extremely Dense		
Outcome	2 vs 1 y	3 vs 2 y	No. of Invasive Breast Cancers	2 vs 1 y	3 vs 2 y	No. of Invasive Breast Cancers	2 vs 1 y	3 vs 2 y	No. of Invasive Breast Cancers
Age 40–49 y									
Advanced stage[a]			443			900			317
OR (95% CI)	0.76 (0.44–1.33)	0.99 (0.45–2.18)		1.32 (0.93–1.88)	0.82 (0.48–1.39)		1.89 (1.06–3.39)	0.95 (0.43–2.10)	
Tumor size 320 mm[b]			451			901			313
OR (95% CI)	0.88 (0.55–1.41)	1.27 (0.67–2.40)		1.02 (0.73–1.41)	1.27 (0.80–2.01)		2.39 (1.37–4.18)	0.53 (0.24–1.18)	
Positive lymph nodes[c]			447			905			316
OR (95% CI)	1.19 (0.75–1.89)	0.95 (0.50–1.78)		1.20 (0.88–1.65)	1.00 (0.64–1.57)		1.34 (0.77–2.31)	1.17 (0.54–2.50)	
	Fatty			Scattered Fibroglandular			Heterogeneously Dense and Extremely Dense		
Age 50–74 y (no HT)									
Advanced stage[a]			193			1774			1778
OR (95% CI)	0.74 (0.24–2.28)	1.05 (0.20–5.50)		1.03 (0.76–1.41)	0.72 (0.41–1.24)		1.21 (0.92–1.61)	0.96 (0.60–1.55)	
Tumor size >20 mm[b]			191			1757			1787
OR (95% CI)	1.36 (0.51–3.62)	0.55 (0.12–2.47)		1.20 (0.92–1.56)	1.06 (0.70–1.63)		1.10 (0.86–1.42)	1.18 (0.78–1.78)	
Positive lymph nodes[c]			194			1785			1793
OR (95% CI)	0.75 (0.30–1.88)	0.43 (0.08–2.31)		1.04 (0.80–1.35)	1.03 (0.67–1.58)		1.14 (0.88–1.46)	1.31 (0.88–1.97)	
Age 50–74 y (combination HT)									
Advanced stage[a]			…			262			537
OR (95% CI)	…	…		0.80 (0.27–2.38)	0.75 (0.08–6.80)		1.56 (0.88–2.80)	1.24 (0.51–3.03)	
Tumor size >20 mm[b]			…			253			535
OR (95% CI)	…	…		0.77 (0.31–1.92)	1.17 (0.27–5.01)		1.59 (0.97–2.61)	1.93 (0.91–4.06)	
Positive lymph nodes[c]			…			263			541
OR (95% CI)	…	…		0.67 (0.29–1.55)	0.99 (0.24–4.02)		1.05 (0.64–1.72)	1.68 (0.77–3.64)	

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	Breast Density and Screening Interval								
	Fatty and Scattered Fibroglandular Densities			Heterogeneously Dense			Extremely Dense		
Outcome	2 vs 1 y	3 vs 2 y	No. of Invasive Breast Cancers	2 vs 1 y	3 vs 2 y	No. of Invasive Breast Cancers	2 vs 1 y	3 vs 2 y	No. of Invasive Breast Cancers
Age 50–74 y (E)									
Advanced stage[a]			…			263			418
OR (95% CI)	…	…		1.14 (0.50–2.61)	1.85 (0.45–7.55)		1.19 (0.66–2.13)	0.83 (0.26–2.63)	
Tumor size >20 mm[b]			…			262			417
OR (95% CI)	…	…		1.56 (0.77–3.15)	2.39 (0.69–8.32)		1.30 (0.78–2.14)	0.64 (0.24–1.68)	
Positive lymph nodes[c]			…			262			423
OR (95% CI)	…	…		1.30 (0.68–2.51)	1.02 (0.32–3.30)		1.28 (0.78–2.10)	0.51 (0.18–1.42)	

Abbreviations: E, estrogen; combination HT, estrogen plus progestogen; HT, hormone therapy; OR, odds ratio; ellipses, not estimable because of small sample size.

[a]Referent: early-stage disease.

[b]Referent: tumor size 20 mm or less.

[c]Referent: negative lymph nodes.

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Table 4

Population Characteristics for Women Without Breast Cancer Who Underwent Screening Mammography Between 1994 and 2008

	Breast Density			
Characteristic	**Fatty**	**Scattered Fibroglandular Densities**	**Heterogeneously Dense**	**Extremely Dense**
Total No. of Women[a]	83 862	407 417	352 431	78 914
Age, %				
40–49 y	19.4	27.6	41.0	55.1
50–59 y	36.2	39.5	38.9	33.5
60–69 y	31.0	23.7	15.0	8.7
70–74 y	13.4	9.3	5.1	2.7
Race/ethnicity, %				
White, non-Hispanic	75.5	78.5	78.9	79.3
Black, non-Hispanic	7.5	7.3	6.8	4.9
Hispanic	11.8	9.2	7.9	6.8
Asian/Pacific Islander	2.0	2.6	4.5	7.4
American Indian/Alaska Native	2.1	1.4	0.7	0.5
Other, includes mixed	1.2	1.1	1.2	1.2
BMI, %				
Underweight (<18.5)	0.5	0.9	1.8	5.1
Normal (18.5–24.9)	19.4	35.5	54.0	71.1
Overweight (25.0–29.9)	30.4	33.2	28.5	17.7
Obese I (30.0–34.9)	24.6	18.3	10.7	4.5
Obese II/III (≥35.0)	25.2	12.1	5.0	1.6
First-degree family history, %				
Yes	12.3	12.3	12.9	13.0
No	87.7	87.7	87.1	87.0
Current hormone therapy use, %				
Yes	29.0	31.4	31.8	26.8
No	71.0	68.6	68.2	73.2

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a]Includes women with first, annual, biennial or triennial screening intervals.

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Table 5

Percentage of False-Positive Recall and False-Positive Biopsy Recommendation at First Mammography and Percentage of Women With at Least 1 False-Positive Recall and False-Positive Biopsy Recommendation After 10 Years of Subsequent Mammography[a]

	% (95% CI)							
	False-Positive Recall[b]				False-Positive Biopsy Recommendation[c]			
Variable	Fatty	Scattered Fibroglandular Densities	Heterogeneously Dense	Extremely Dense	Fatty	Scattered Fibroglandular Densities	Heterogeneously Dense	Extremely Dense
Age 40–49 y[d]								
First mammography	11.2 (10.3–12.2)	17.0 (16.6–17.4)	18.0 (17.6–18.4)	15.1 (14.4–15.8)	1.6 (1.3–2.1)	2.4 (2.2–2.6)	2.4 (2.2–2.6)	2.1 (1.8–2.4)
Cumulative probability of false-positive after 10 y[e]								
1-y Screening interval	36.3 (34.3–38.3)	60.0 (58.6–61.3)	68.9 (67.6–70.1)	65.5 (64.0–66.9)	5.5 (4.5–6.7)	9.3 (8.3–10.4)	12.3 (11.0–13.7)	12.3 (10.9–13.8)
2-y Screening interval	21.2 (20.0–22.3)	38.5 (37.8–39.3)	46.3 (45.5–47.1)	43.2 (42.3–44.1)	2.9 (2.4–3.4)	4.9 (4.6–5.3)	6.6 (6.1–7.1)	6.6 (6.0–7.1)
3-y Screening interval	14.2 (13.4–15.1)	27.0 (26.3–27.6)	33.1 (32.3–33.9)	30.6 (29.8–31.4)	2.0 (1.7–2.4)	3.4 (3.1–3.7)	4.5 (4.2–4.9)	4.5 (4.1–4.9)
Age 50–74 y (no HT)[f]								
First mammography	9.9 (9.1–10.8)	16.5 (16.0–17.1)	19.0 (18.2–19.8)	16.3 (14.3–18.5)	2.4 (2.0–2.9)	3.2 (2.9–3.4)	3.8 (3.4–4.2)	3.3 (2.4–4.6)
Cumulative probability of false-positive after 10 y[e]								
1-y Screening interval	30.3 (29.3–31.3)	49.8 (49.0–50.6)	60.2 (59.3–61.0)	58.5 (57.1–59.8)	5.0 (4.5–5.6)	8.1 (7.6–8.6)	10.8 (10.2–11.6)	11.2 (10.2–12.4)
2-y Screening interval	17.4 (16.8–18.0)	30.7 (30.2–31.2)	38.9 (38.3–39.5)	37.5 (36.6–38.4)	2.8 (2.5–3.1)	4.5 (4.3–4.8)	6.1 (5.8–6.5)	6.3 (5.8–6.9)
3-y Screening interval	12.1 (11.6–12.6)	21.9 (21.3–22.4)	28.2 (27.6–28.9)	27.1 (26.3–27.9)	2.1 (1.9–2.4)	3.4 (3.2–3.7)	4.7 (4.3–5.0)	4.8 (4.4–5.3)
Age 50–74 (combination HT)[g]								
First mammography	11.1 (8.4–14.6)	18.5 (16.8–20.4)	19.6 (17.5–21.8)	14.7 (10.7–19.7)	1.9 (0.9–4.0)	2.8 (2.1–3.7)	2.1 (1.4–3.0)	2.9 (1.4–6.0)
Cumulative probability of false-positive after 10 y[e]								
1-y Screening interval	34.4 (32.7–36.2)	58.6 (57.5–59.8)	68.1 (67.0–69.2)	65.8 (64.2–67.4)	6.0 (5.0–7.1)	9.8 (8.9–10.8)	12.7 (11.6–13.9)	14.3 (12.7–16.2)
2-y Screening interval	19.7 (18.7–20.8)	37.1 (36.3–37.9)	45.3 (44.4–46.2)	43.2 (41.9–44.5)	3.0 (2.5–3.6)	5.0 (4.6–5.4)	6.5 (6.0–7.1)	7.4 (6.6–8.3)
3-y Screening interval	12.9 (12.1–13.7)	25.3 (24.4–26.2)	31.6 (30.5–32.7)	30.0 (28.8–31.2)	1.8 (1.5–2.2)	3.1 (2.7–3.5)	4.0 (3.6–4.6)	4.6 (4.0–5.3)
Age 50–74 y (E)[h]								
First mammography	10.0 (6.5–15.2)	15.3 (13.2–17.8)	19.0 (16.1–22.4)	18.8 (11.7–28.8)	1.6 (0.5–5.0)	2.8 (1.9–4.1)	4.0 (2.7–6.0)	3.8 (1.2–11.2)
Cumulative probability of false-positive after 10 y[e]								
1-y Screening interval	32.9 (30.3–35.6)	52.1 (50.2–54.0)	60.1 (58.2–62.0)	56.7 (53.8–59.5)	5.8 (4.4–7.5)	8.8 (7.5–10.2)	10.1 (8.7–11.8)	8.2 (6.4–10.3)

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	% (95% CI)							
	False-Positive Recall[b]				False-Positive Biopsy Recommendation[c]			
Variable	Fatty	Scattered Fibroglandular Densities	Heterogeneously Dense	Extremely Dense	Fatty	Scattered Fibroglandular Densities	Heterogeneously Dense	Extremely Dense
2-y Screening interval	19.0 (17.5–20.6)	32.4 (31.3–33.5)	38.7 (37.4–40.0)	35.9 (34.0–37.9)	3.1 (2.5–4.0)	4.8 (4.3–5.4)	5.6 (5.0–6.3)	4.5 (3.7–5.5)
3-y Screening interval	13.0 (11.9–14.3)	22.8 (21.6–24.1)	27.7 (26.3–29.2)	25.5 (23.9–27.2)	2.4 (1.8–3.0)	3.6 (3.1–4.3)	4.2 (3.6–4.9)	3.4 (2.7–4.1)

Abbreviations: Combination HT, estrogen plus progestogen; E, estrogen; HT, hormone therapy.

[a] First mammography includes examinations among women with no prior mammograms in the Breast Cancer Surveillance Consortium (BCSC) database, no indication of comparison films, and no self-report of a prior mammogram. Subsequent mammography includes examinations that occur after a first screening examination. All estimates are adjusted for BCSC registry.

[b] No invasive carcinoma or ductal carcinoma in situ (DCIS) diagnosis within 1 year after a positive screening examination result or before the next screening examination, whichever occurred first.

[c] No invasive carcinoma or DCIS diagnosis within 1 year after a positive screening examination result with a recommendation for biopsy.

[d] First mammography false-positive recall calculated for 81 359 screening examinations ($P < .001$ per Wald test across density categories), and for false-positive biopsy recommendation calculated for 79 346 screening examinations ($P = .006$ per Wald test across density categories). Cumulative probability of false-positive recall for mammography calculated for 580 729 screening examinations and for false-positive biopsy recommendation calculated for 620 723 screening examinations.

[e] $P < .001$ per Wald test across all density categories and for recall and biopsy.

[f] First mammography false-positive recall calculated for 31 348 screening examinations ($P < .001$ per Wald test across density categories), and for false-positive biopsy recommendation calculated for 30 308 screening examinations ($P < .001$ per Wald test across density categories). Cumulative probability of false-positive recall for mammography calculated for 849 103 screening examinations and for false-positive biopsy recommendation calculated for 941 994 screening examinations.

[g] First mammography false-positive recall calculated for 3695 screening examinations ($P < .001$ per Wald test across density categories), and for false-positive biopsy recommendation calculated for 3605 screening examinations ($P = .54$ per Wald test across density categories). Cumulative probability of false-positive recall for mammography calculated for 355 889 screening examinations and for false-positive biopsy recommendation calculated for 392 723 screening examinations.

[h] First mammography false-positive recall calculated for 1797 screening examinations ($P = .02$ per Wald test across density categories), and for false-positive biopsy recommendation calculated for 1755 screening examinations ($P = .37$ per Wald test across density categories). Cumulative probability of false-positive recall for mammography calculated for 172 780 screening examinations and for false-positive biopsy recommendation calculated for 188 009 screening examinations.