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One vs. Two Breast Density Measures to Predict 5- and 10- Year Breast Cancer Risk

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Abstract

Background—One measure of Breast Imaging Reporting and Data System (BI-RADS) breast density improves 5-year breast cancer risk prediction, but the value of sequential measures is unknown. We determined if two BI-RADS density measures improves the predictive accuracy of the Breast Cancer Surveillance Consortium 5-year risk model compared to one measure.

Methods—We included 722,654 women aged 35–74 years with two mammograms with BI-RADS density measures on average 1.8 years apart; 13,715 developed invasive breast cancer. We used Cox regression to estimate the relative hazards of breast cancer for age, race/ethnicity, family history of breast cancer, history of breast biopsy, and one or two density measures. We developed a risk prediction model by combining these estimates with 2000–2010 Surveillance, Epidemiology, and End Results incidence and 2010 vital statistics for competing risk of death.

Results—The two-measure density model had marginally greater discriminatory accuracy than the one-measure model (AUC=0.640 vs. 0.635). Of 18.6% of women (134,404/722,654) who decreased density categories, 15.4% (20,741/134,404) of women whose density decreased from heterogeneously or extremely dense to a lower density category with one other risk factor had a clinically meaningful increase in 5-year risk from <1.67% with the one-density model to ≥1.67% with the two-density model.

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Conclusion—The two-density model has similar overall discrimination to the one-density model for predicting 5-year breast cancer risk and improves risk classification for women with risk factors and a decrease in density.

Impact—A two-density model should be considered for women whose density decreases when calculating breast cancer risk.

Keywords

Breast density; breast cancer risk

Introduction

Breast density is one of strongest risk factors for breast cancer and provides important information for risk assessment. Breast Imaging Reporting and Data System (BI-RADS) (1) breast density has been shown to improve the discriminatory accuracy in two breast cancer risk prediction models (2, 3). Inter-rater agreement of BI-RADS breast density assessment is moderate and has raised concern about using this subjective measure of density in risk prediction models to evaluate individual risk (4–8). Misclassification of BI-RADS categories could result in an under- or overestimation of breast cancer risk.

Our prior work (9) showed an increase in BI-RADS breast density category is associated with an increase in breast cancer risk, and a decrease in density with a decrease in risk, within one year of the most recent mammogram. Reductions in breast density after 12–20 months of tamoxifen therapy have been associated with reduced risk of breast cancer among high-risk women, and reduced risk of 2nd breast cancer events in breast cancer survivors (10, 11).

We developed a 5-year and 10-year breast cancer risk prediction model that uses the same risk factors as the BCSC risk model, but included two measures of BI-RADS breast density instead of one, to assess if sequential density measures can improve risk prediction by providing a more precise density assessment and/or enable evaluation of changes in breast density that influence breast cancer risk.

Materials and Methods

Study Setting and Data Sources

Data were pooled from seven mammography registries that participate in the Breast Cancer Surveillance Consortium (12) (http://breastscreening.cancer.gov). Registries collect data including patient characteristics and clinical information from community radiology facilities. Breast cancer diagnoses are obtained by linking women in the BCSC to pathology databases; regional Surveillance, Epidemiology, and End Results (SEER) programs; and state tumor registries with completeness of reporting estimated at >94.3% (13). Vital status is obtained through linkage to SEER registries, state tumor registries, and the state death tapes. Data are pooled at a Statistical Coordinating Center. Registries and the Coordinating Center have received Institutional Review Board approval for active or passive consenting processes or a waiver of consent to enroll participants, link data, and perform analyses. 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

The study sample included women aged 35–74 years who had at least two mammograms with non-missing BI-RADS density between January 1994 through December 2010. We excluded women with a history of ductal carcinoma *in situ* (DCIS) or invasive breast cancer, breast implants or mastectomy prior to the second mammogram. We selected a woman's earliest pair of screening or diagnostic mammograms for which the time between mammograms was ≥ 9 months and ≤ 4 years for a sample of mammograms on average 1 to 2 years apart, consistent with the recommended screening frequency in the U.S. (14), and for which family history of breast cancer, history of benign breast biopsy, and race/ethnicity were non-missing at the second examination (see Supplemental Figure). Women diagnosed with DCIS or invasive breast cancer the three months following their second examination were also excluded. Our study population had similar distributions of age, race/ethnicity, breast density, and family history of breast cancer as the distributions among all women in the BCSC (data not shown).

Measurements and Definitions

Demographic and breast health history information were obtained on a self-administered questionnaire completed at each mammography examination. We obtained self-reported information on history of first-degree relatives (mother, sister, or daughter) with breast cancer, history of breast biopsy, and race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian/Native Hawaiian/Pacific Islander, Native American/Native Alaskan, or other/mixed race).

Radiologists categorized breast density at the time of clinical interpretation of the mammogram, as part of clinical practice, using American College of Radiology's BI-RADS breast density categories (1): (a) almost entirely fat, (b) scattered fibroglandular densities, (c) heterogeneously dense, or (d) extremely dense. We classified women into 1 of 16 possible density combinations based on the densities assigned at the two examinations.

Women were considered to have breast cancer if diagnosed with invasive carcinoma during the follow-up period.

Statistical Analysis/Model development

Risk factor frequency distributions were determined for women with and without breast cancer. We used Cox proportional hazards regression to model time to invasive breast cancer for the same covariates included in the BCSC risk model (2): age at entry (linear and quadratic terms), race/ethnicity, history of first-degree relatives with breast cancer, history of benign breast biopsy. We also included interaction terms between age at entry (linear) and BI-RADS density, first-degree relatives with breast cancer, and race/ethnicity and between age at entry (quadratic) and first-degree relatives with breast cancer. Age was modeled using linear and quadratic terms because breast cancer incidence increases non-linearly with age.

We fit two models. In the first model, we used the BI-RADS density assessment from the woman's most recent mammogram. In the second model, we included both density assessments. All other covariates were assessed at a woman's most recent mammogram. Follow-up time started three months after the most recent mammogram. Women were censored at the time of death, diagnosis of DCIS, mastectomy, end of complete cancer follow-up by mammography registries, or 10 years after study entry. We assessed the proportional hazards assumption by calculating interval-specific hazard ratios (i.e., 0–3 months, 3–6 months, 6 months-1 year, 1 year-2 years, etc.), which appeared consistent over time for each predictor variable.

We estimated and plotted the cumulative incidence of invasive cancer by the most recent BI-RADS density measure and by the 16 combinations of two BI-RADS density measures accounting for the competing risks of DCIS diagnosis, mastectomy, and death.

We developed absolute risk models to estimate the 5 and 10-year risk of invasive breast cancer based on one and two density measures in addition age, race/ethnicity, family history, and history of benign breast biopsy. We estimated the baseline breast cancer risk from the age- and race/ethnicity-specific incidence of invasive breast cancer from the SEER 18 registries (2000–2010), which provide the most representative data for the US population (15). For each race/ethnicity group, we estimated age-specific incidence by fitting a third order polynomial model to the SEER data. We used the methods described in Gail et al (16) for translating the hazard ratios and risk factor distributions into absolute risks. We estimated the age- and race/ethnicity-specific distributions needed to standardize hazard ratios to be relative to average risk using data from a larger set of 4,610,085 mammograms from the BCSC. Specifically, we used logistic regression to model BI-RADS density, history of first-degree relatives with breast cancer, and history of benign breast biopsy as a function of age (linear and quadratic terms), race/ethnicity, and an interaction between race/ethnicity and age (linear term), among women aged 40 and older. We used the model-predicted probabilities to estimate the proportion of women in each age, race/ethnicity, and predictor category to adjust the hazard ratios to be relative to average risk. The age- and race/ethnicity-specific competing risk of death for women was calculated using 2010 U.S. Vital Statistics (17). Age-specific mortality for each race/ethnicity group was estimated by fitting an exponential model to the all-cause mortality rates, adjusted for mortality due to breast cancer. The age- and race/ethnicity-specific competing risk of DCIS was estimated by fitting separate models by race/ethnicity with a third-order polynomial effect of age to SEER breast *in situ* rates. We applied the adjustments for whites to women of other/mixed race for whom insufficient data were available.

We assessed model calibration by calculating the ratio of the expected breast cancer rate from the absolute risk model (E) to the observed breast cancer rate (O) by age group, race/ethnicity, and individual risk factor distributions. We used the Kaplan-Meier estimator to estimate the observed rate within each subgroup to take into account censoring (18). We assumed that both the observed and the expected number of breast cancers follow a Poisson distribution and calculated the 95% confidence interval for E/O and 5- and 10-year risk of breast cancer as follows: (E/O)*exp(±1.96*1/sqrt(observed number of breast cancers)) and 5- and 10-year risk ± 1.96*100*sqrt(expected number of breast cancers)/number of women

in the subgroup, where the expected number of breast cancers is equal to the number of women in the subgroup*5- and 10-year risk/100.

We used risk reclassification tables (19, 20) to compare the performance of the two-measure vs. one-measure density models. Women were cross-classified based on their risks estimated by the Breslow estimator of the 5-year survivor function from the two Cox models (21), using risk categories 0 to 1.66%, 1.67 to 3%, and >3%. We used the Kaplan-Meier estimator to estimate the number of breast cancer events and nonevents at 5 years within each cross-classified risk category, as in French et al (18).

The discriminatory accuracy of the model was summarized using the area under the time-dependent receiver operating characteristic curve (AUC) (22) at 5 years and 10 years, with absolute risk as the marker. We performed 5-fold cross-validation to confirm the internal validity of the model (23, 24). AUCs were calculated separately for all women and for the subset of women whose BI-RADS density category changed from their previous to their most recent mammogram. All analyses were performed using SAS (version 9.3, SAS Institute, Cary, NC) and R (version 3.0.3, R Foundation for Statistical Computing, Vienna, Austria). The survival ROC package (25) was used to estimate time-dependent receiver operating characteristic curves. The cmprsk package (26) was used to estimate cumulative incidence functions for invasive breast cancer in the presence of competing risks.

Results

We included 722,654 women aged 35–74 years who underwent two mammograms with BI-RADS density measures on average 1.8 years (range 0.75–4 years) apart; 13,715 developed invasive breast cancer during a mean of 6.6 years of follow-up (range, 1 day to 10 years). The overall 5- and 10-year cumulative incidences were 1.32% and 2.87%, respectively. Women with invasive breast cancer were more likely to be older, white, have a family history of breast cancer, and have heterogeneously or extremely dense breasts (Table 1). A total of 63.5% of women had the same BI-RADS density on two sequential examinations while 17.9% had an increase in breast density category and 18.6% had a decrease. The most common combinations of changing density categories were heterogeneously dense on the earlier examination and scattered fibroglandular on the most recent examination (10.0%) and scattered fibroglandular densities on the earlier examination and heterogeneously dense on the most recent examination (9.9%).

Figures 1a–1d show the 10-year cumulative incidence curves of invasive breast cancer for the combinations of BI-RADS density measures. Women with fatty breasts on their most recent mammogram had similar low risks of breast cancer regardless of previous density measures. Women with scattered fibroglandular densities on their most recent mammogram and prior density of heterogeneously dense (10% of screened women) or extremely dense (0.6% of screened women) were at higher risk of breast cancer than those women whose density remained scattered fibroglandular densities on both exams. By contrast, women with scattered fibroglandular densities on their most recent mammogram and prior density of almost entirely fat (3.5% of screened women) were at lower risk of breast cancer than those women whose density remained scattered fibroglandular densities on both exams. Women

with heterogeneously dense breasts on their most recent mammogram and prior density of extremely dense (4.2% of screened women) were at higher risk of breast cancer than those women whose density remained heterogeneously dense. Conversely, women with heterogeneously dense breasts on their most recent mammogram and prior density of scattered fibroglandular densities (9.9% of screened women) were at lower risk of breast cancer than those women whose breast density remained heterogeneously dense. Women with extremely dense breasts on their most recent mammogram had a high risk of breast cancer regardless of previous density measures.

In general, the strength of the breast density association with breast cancer was greatest for women with extremely dense breasts on a recent or previous mammogram and lowest for women with almost entirely fatty breasts on a recent or previous mammogram relative to women who had scattered fibroglandular densities on two sequential mammograms (Table 2). The strength of the breast density association with breast cancer decreased significantly with increasing age; for example, the hazard ratio (HR) for extremely dense vs. scattered fibroglandular tissue decreased from 2.1 (95% CI 1.9, 2.3) for women 35–49 to 1.3 (95% CI 1.2, 1.5) for women 65 years and older (data not shown). The strength of the family history association with breast cancer also tended to decrease with increasing age, for example, from HR of 1.8 (95% CI 1.6, 1.9) for women aged 35–49 to HR 1.5 (95% CI 1.4, 1.6) for women aged 65 and older, although this interaction was only borderline statistically significant (p-values for tests of interaction with linear and quadratic age = 0.09 and 0.15, respectively).

The two-measure density 5-year risk model was well calibrated overall (Table 3). The two-measure density model discrimination, as measured by the area under the receiver operating characteristic curve (AUC), was 0.640 (0.639 from 5-fold cross-validation) and was marginally greater than that of the one-measure density model AUC of 0.635 (0.635 from 5-fold cross-validation). Similar results were observed for the 10-year two- and one-measure density models; AUC 0.628 and 0.622, respectively. Among women who changed density categories, discrimination for the two-measure density 5-year risk model was 0.641 (0.639 from 5-fold cross-validation and for the one-measure density model 0.630 (0.629 from 5-fold cross-validation). Calibration of the two-measure density 5-year risk model was reasonably accurate across risk factor subgroups (Table 3). The model was well calibrated across family history of breast cancer and history of benign breast biopsy. As expected, the predicted absolute risks of breast cancer were lower than the breast cancer rates observed in the BCSC in younger women and among Asian women. Also, predicted risks were lower than observed BCSC breast cancer rates for rare changes in density combinations such as extremely dense and fatty breasts and higher than observed for women with fatty breasts on both examinations.

Table 4 presents the predicted 5-year risk by breast density groups and subgroups defined by the presence or absence of other risk factors that can be used to determine how changes in density measures between examinations can impact risk among subgroups. For example, women with scattered fibroglandular densities on the most recent examination and heterogeneously dense breasts on the previous examination with a family history of breast cancer would have a 5-year risk of 1.62% if the most recent density measure were used to

calculate risk, and 1.83% with the two-measure model. Of 18.6% (134,404/722,654) of women who decreased density categories, 15.4% (20,741/134,404) had a clinically meaningful increase in 5-year risk; women whose density decreased from heterogeneously or extremely dense to a lower category with a family history of breast cancer or history of breast biopsy had an increase in 5-year risk from <1.67% with the one-density model to ≥1.67% with the two-density model (bold numbers in Table 4). By contrast a small percentage of women had a clinically meaningful change in risk if breast density increased; of the 17.9% (129,690/722,654) of women who increased density categories, 0.6% (751/129,690) decreased 5-year risk from ≥1.67% with the one-density model to <1.67% with the two-density model if the prior density was fatty and women had a family history of breast cancer or history of breast biopsy (italicized numbers in Table 4). Women with fatty breast density on their most recent mammogram and no other breast cancer risk factors had 5-year risks <1.67% regardless of previous breast density measures.

Among women who had a change in density categories between examinations, we calculated the proportion of women reclassified correctly (cancer cases to a higher risk category, non-cases to a lower risk category) and the proportion of women reclassified incorrectly. Using a cutpoint of ≥1.67% to define high risk, there was a slight increase in the proportion of women diagnosed with breast cancer who had risk ≥1.67% (42.3% one-measure and 44.5% two-measures), a similar proportion not diagnosed with breast cancer who had risk ≥1.67% (25.6% for one-measure and 26.2% for two measures) and a less than 1% decrease in women not diagnosed with breast cancer who had risk <1.67% (74.5% one-measure and 73.8% two-measures). The positive predictive value increased slightly from 2.19% to 2.24%. The two-measure density model reclassified 6.6% of women to a risk ≥1.67% and 5.9% to a lower risk of <1.67% compared with the one-measure model.

The distributions of 5- and 10-year risk with the two-measure and one-measure density models are shown in Figures 2a–d. Forty percent of women had a 5-year risk that was less than 1% with the two-measure model. Only 3% of women had a 5-year risk that was 3% or greater. The 10-year risk distribution similarly had concentrated numbers of low risk women.

Discussion

The BCSC 5-year risk model has improved discriminatory accuracy compared to models without a measure of breast density and has been validated in a large mammography cohort (2, 27). We evaluated whether two measures of BI-RADS breast density would further improve the discriminatory accuracy of the BCSC 5-year risk model and found that for most women, two measures would not change breast cancer risk sufficiently to impact clinical decisions. However, for the modest fraction of women (18.6%) who experience a decrease in breast density measures between two mammograms on average 1.8 years apart, the use of both measures offers some improvement in risk classification. In some cases, this improvement could affect clinical discussions about supplemental screening for women with dense breasts and discussions of chemoprevention for women with several risk factors.

High interval cancer rates have been reported for women with 5-year BCSC risk of ≥1.67% and extremely dense breasts or 5-year risk >2.50% and heterogeneously dense breasts (28) with recommendations that discussions of supplemental imaging be directed to these women who have the potential to benefit from alternative screening modalities. Women with extremely dense breasts on the most recent examination and almost entirely fatty on the previous examination with a family history of breast cancer or history of breast biopsy would have a 5-year breast cancer risk of 1.93–2.02% if the most recent measure were used to calculated risk (i.e., ≥1.67%) and 1.16–1.65% with the two-measure model (i.e., <1.67%). Similarly, women with heterogeneously dense breasts on the most recent examination and almost entirely fatty on the previous examination with a family history of breast cancer and history of breast biopsy would have 5-year breast cancer risk of 3.01% if the most recent measure were used to calculated risk (i.e., ≥2.50%) and 2.35% with a two-measure model (i.e., <2.50%). Thus, if the two-measure model were used, discussions of alternative screening strategies for women with dense breasts would be avoided for some women.

Accurately identifying women at high risk of breast cancer is important so primary care providers can discuss primary prevention interventions (29, 30). The American Society of Clinical Oncology and National Comprehensive Cancer Network define elevated 5-year risk as ≥1.67 when considering primary prevention with selective estrogen receptor modulators (SERM), while the USPSTF defines elevated 5-year risk as ≥3% (29, 30). Women with scattered fibroglandular densities on the most recent examination and heterogeneously dense breasts on the previous examination with a family history of breast cancer or history of breast biopsy would have a 5-year risk of 1.57–1.62% if the most recent density measure were used to calculate risk (i.e., <1.67%), and 1.79–1.83% with the two-measure model (i.e., ≥1.67%). Similarly, women with a family history of breast cancer, history of breast biopsy, and scattered fibroglandular densities on the most recent examination and extremely dense breasts on the previous examination would have a 5-year risk of 2.44% if the most recent density measure were used to calculate risk (i.e., <3%), and 3.06% with the two-measure model (i.e., ≥3%). Thus, the two-density model can be particularly informative in estimating risk among women with several risk factors to inform patient-provider discussions of prevention interventions.

There is mounting evidence that women with sustained levels of high breast density are at highest risk of breast cancer, those with low levels of breast density over time are at lowest risk and those that change density over time can increase or decrease their risk (9, 31). The IBIS-I has reported for women on tamoxifen that had a reduction in breast density of 10% or more, the risk of breast cancer was significantly reduced 52% relative to controls (10). A study reported improved survival among postmenopausal women with breast cancer with a decrease in breast density on adjuvant tamoxifen (32). Another recent study reported a decrease in risk of contralateral breast cancer among women who have a decrease in breast density within the first two years after breast cancer diagnosis (33). Our results are consistent with these studies. We found women who decrease from a higher density to fatty breasts or decrease from heterogeneously dense to scattered fibroglandular density instead of density remaining unchanged, have a reduction in breast cancer risk. Automated density measures incorporated into the clinical practice setting will be critical to providing reproducible density estimates for evaluating changes in density and risk over time.

Women may be reluctant to engage in risk reduction therapies unless they are confident their breast cancer risk is sufficiently high in the near and/or long term (34). Commonly used breast cancer risk prediction models estimate 5-year risk of breast cancer (2, 16). The Tyrer–Cuzick breast cancer risk model estimates 10-year risk using a complex model that collects 12 personal risk factors and extensive family history information (35, 36), but has not been validated in an average risk population. Our one- and two-measure density models are simple and easy to use and provide moderately accurate estimates of 5- and 10-year risk that can be used in breast cancer prevention discussions to assist women in making clinical decisions.

A major strength of our study is the large number of women with two breast density measures and the large number of breast cancers. Despite this, some groups that changed density category were very small and the numbers of cancers in these groups were few, limiting our ability to estimate risk accurately in these groups. Misclassification and/or changes in breast density reporting could impact women changing density categories. However, studies have found no change in historical distributions of breast density categories from 1996 to 2009 (8, 37). Lastly, for risk prediction modeling, it does not matter if an observed change in density is due to subjective differences in measurements or changes in a woman's breast composition.

In summary, for most women, a risk prediction model that includes two BI-RADS density measures provides minimal improvement over one recent measurement for predicting 5- and 10-year breast cancer risk. However, for those women whose prior BI-RADS density measure varies from the most recent measure, health care providers should take into account both recent and previous breast density measurements when calculating breast cancer risk since estimates could differ and impact clinical decision-making.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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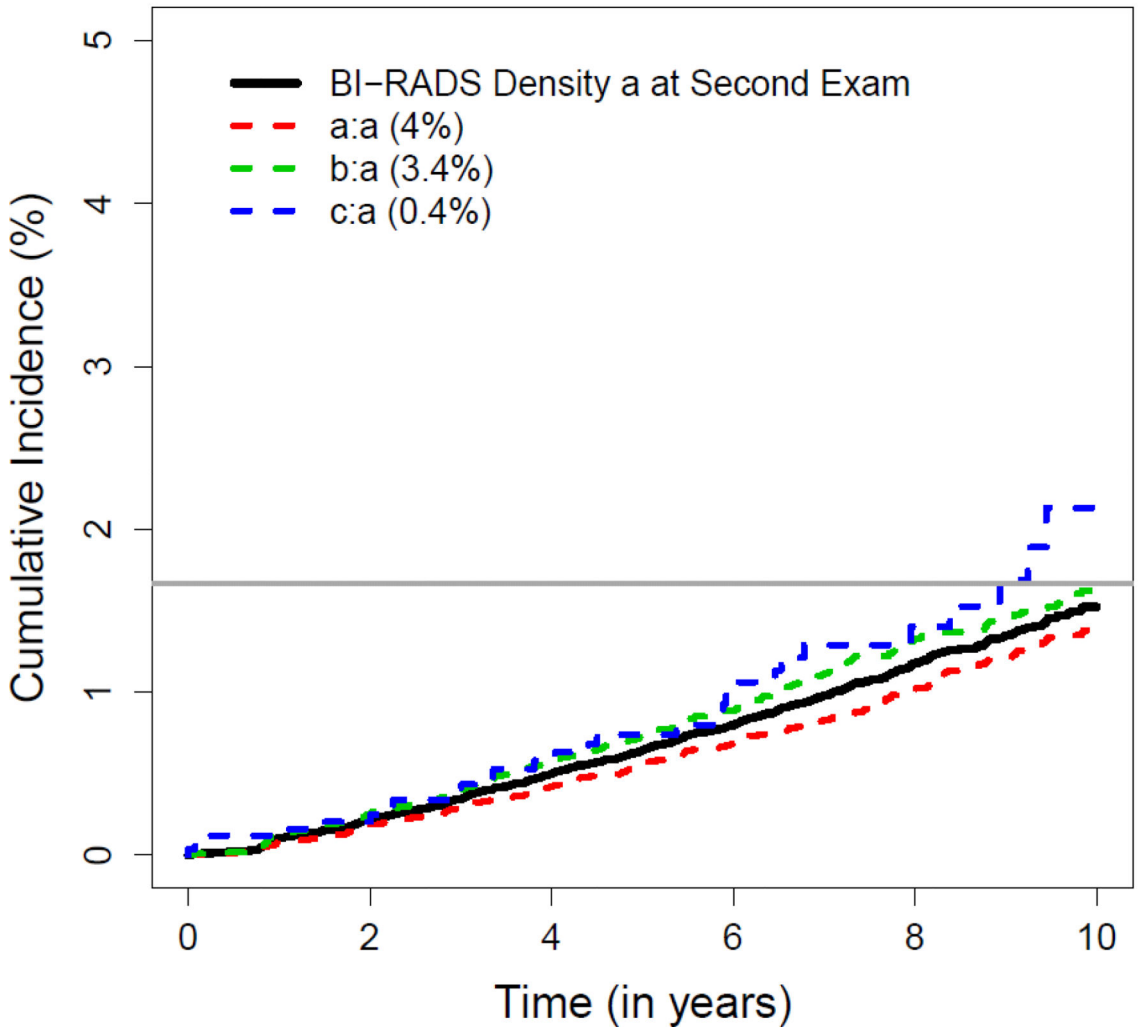
a



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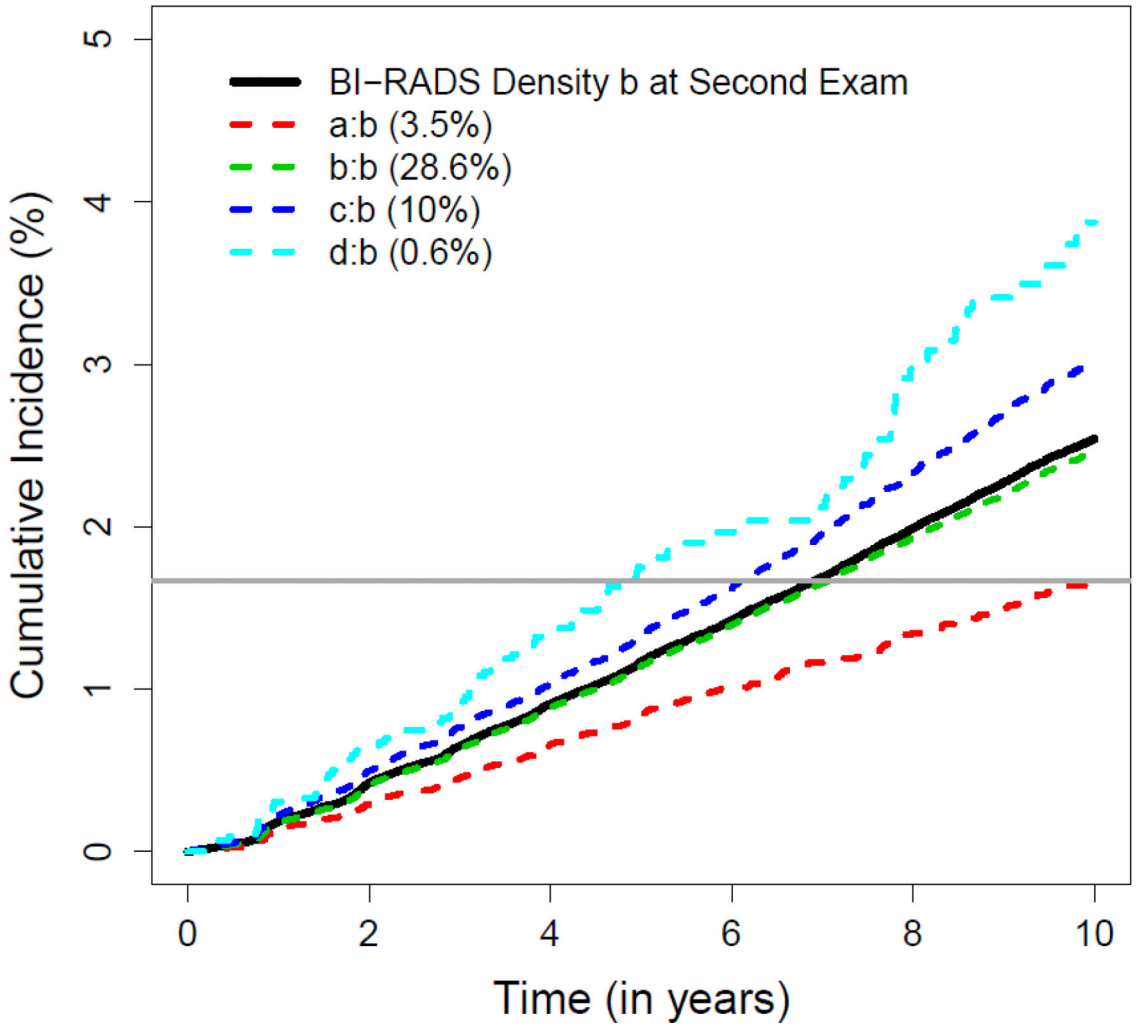

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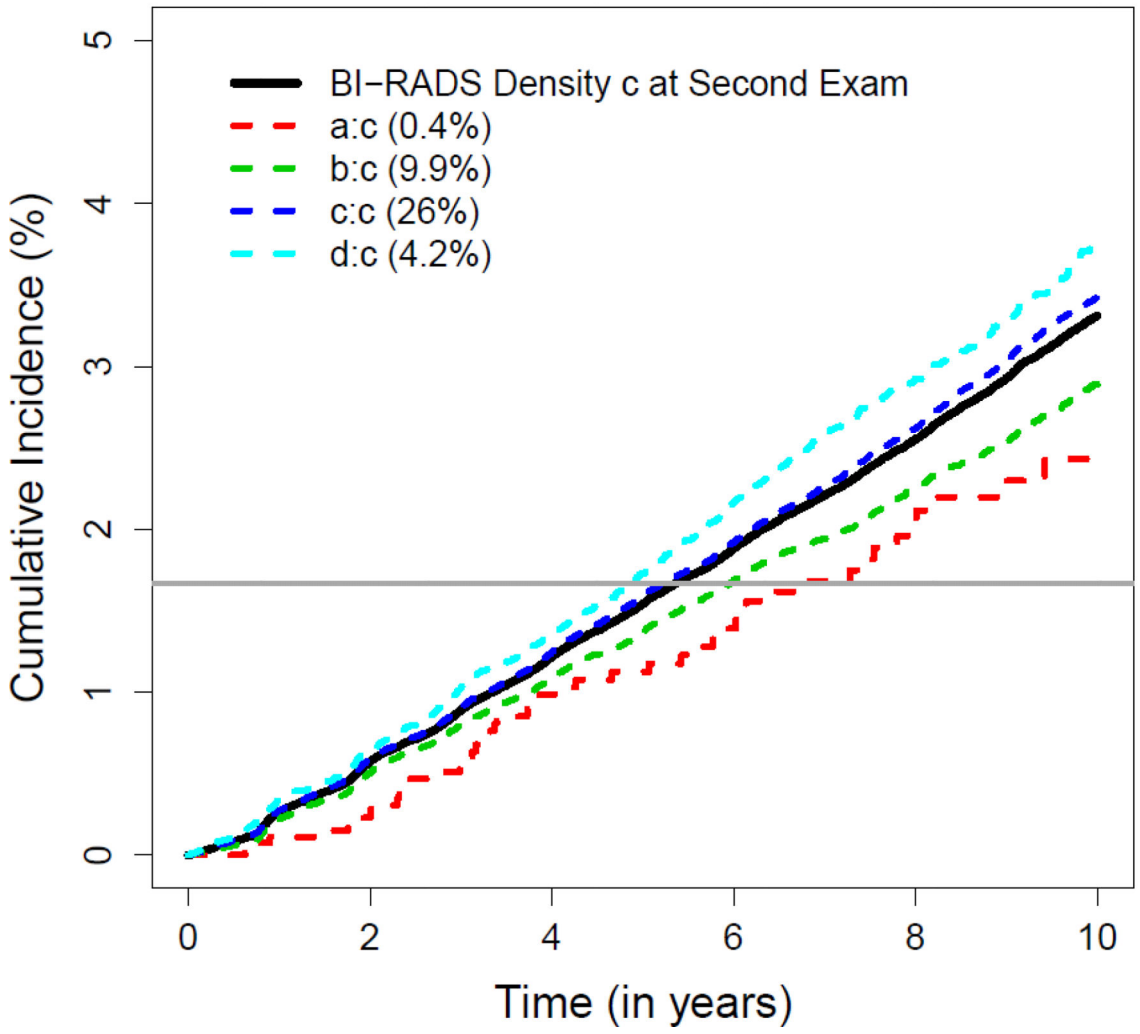

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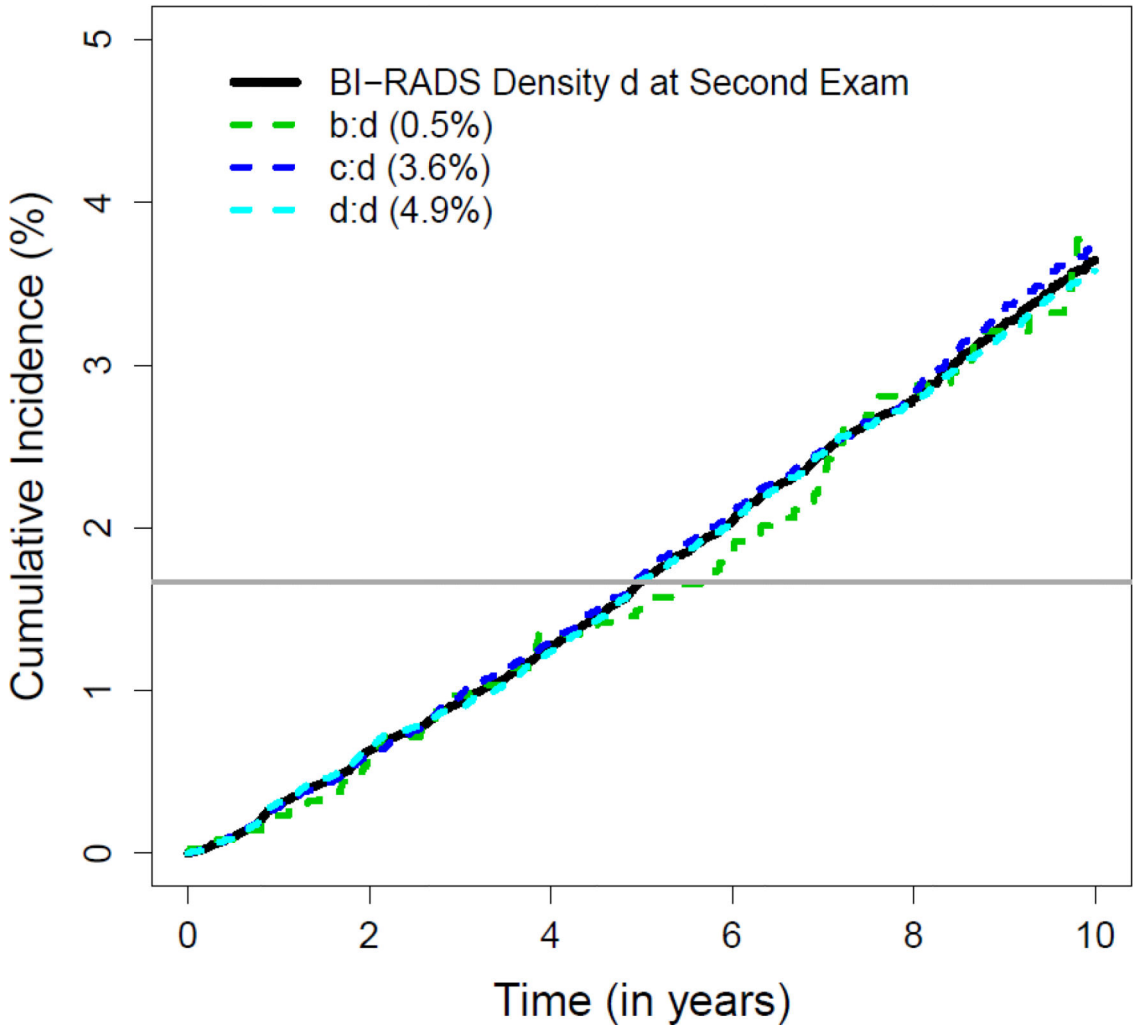
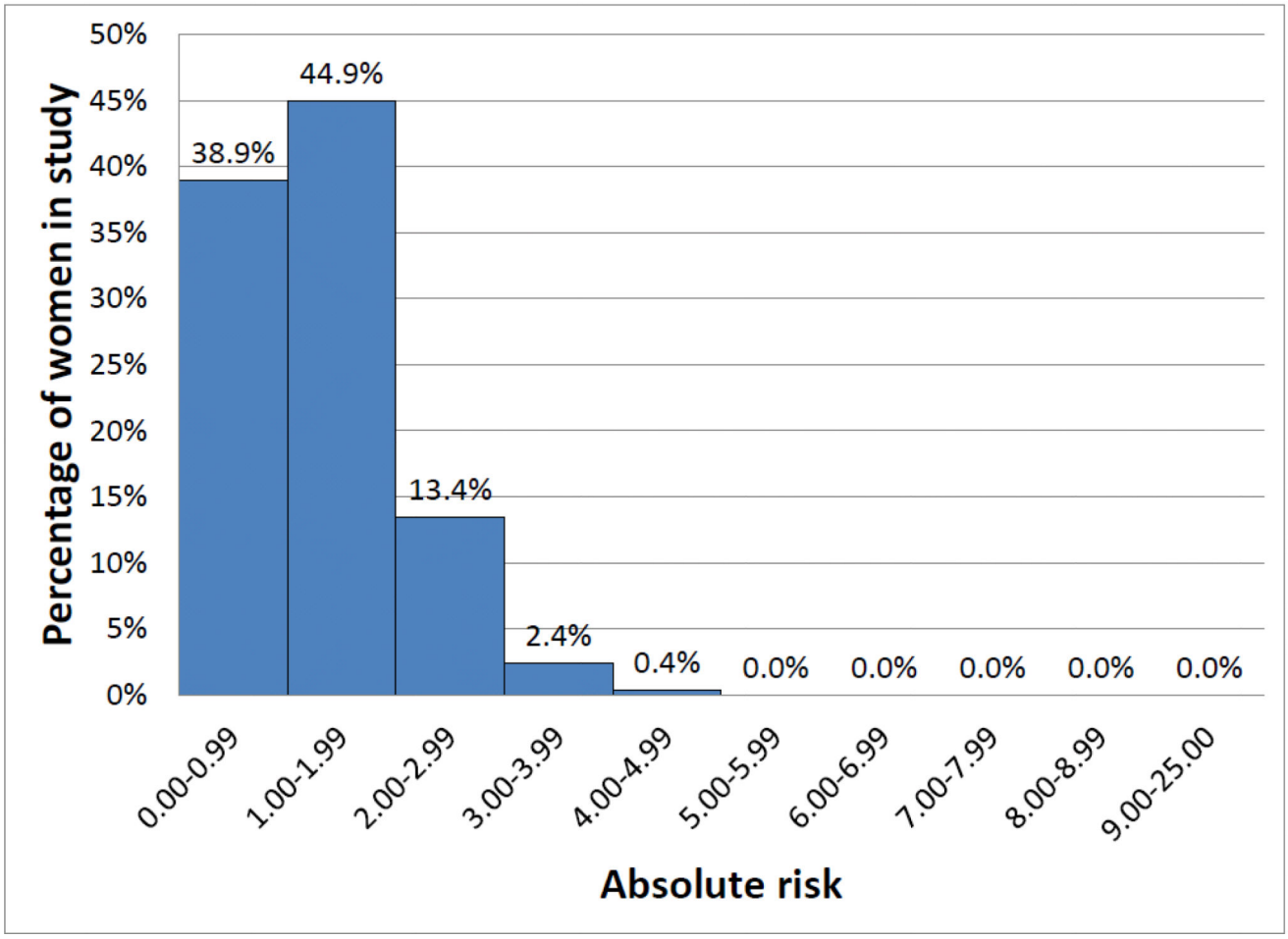


Figure 1.

a–1d. Cumulative incidence of invasive cancer by most recent BI-RADS density measure (Figure 1a; almost entirely fatty breasts, 1b; scattered fibroglandular densities, 1c; heterogeneously dense, 1d; extremely dense) and previous density measure for the 14 combinations of BI-RADS density over 10 years of follow-up. The sold horizontal line represents a cumulative incidence of 1.67%. Density combinations d:a and a:d were excluded from the figure because of small numbers.

a



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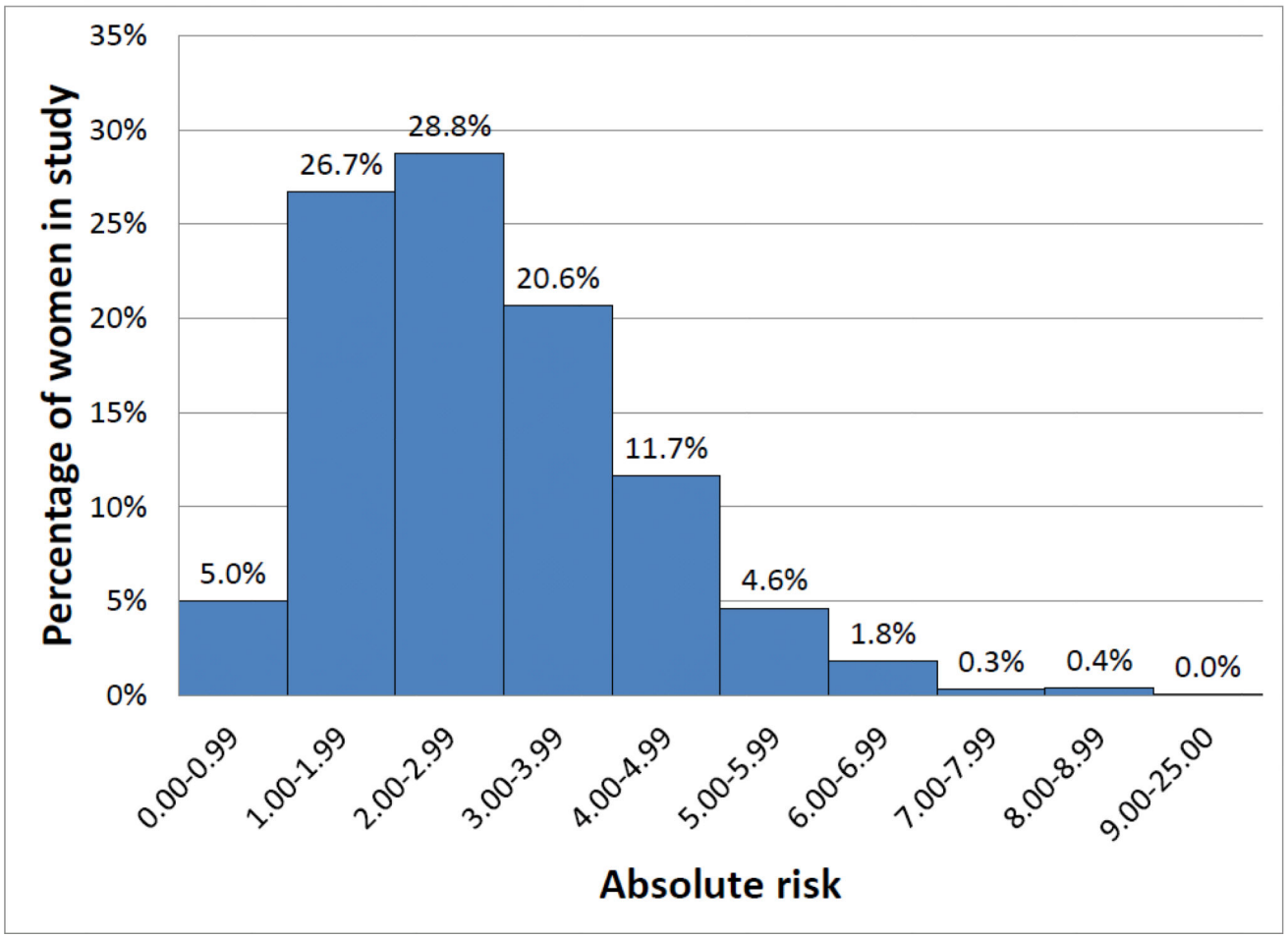

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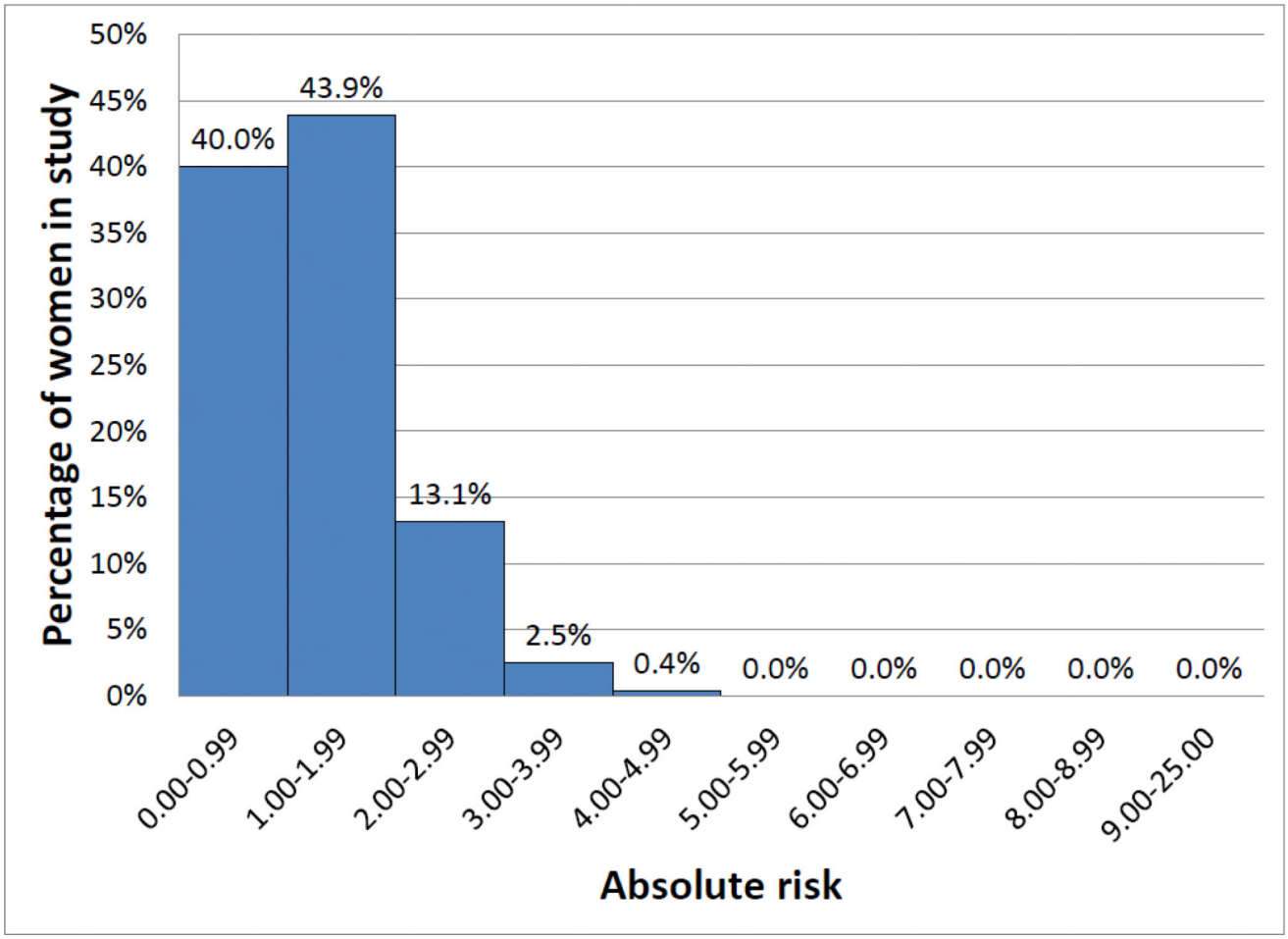

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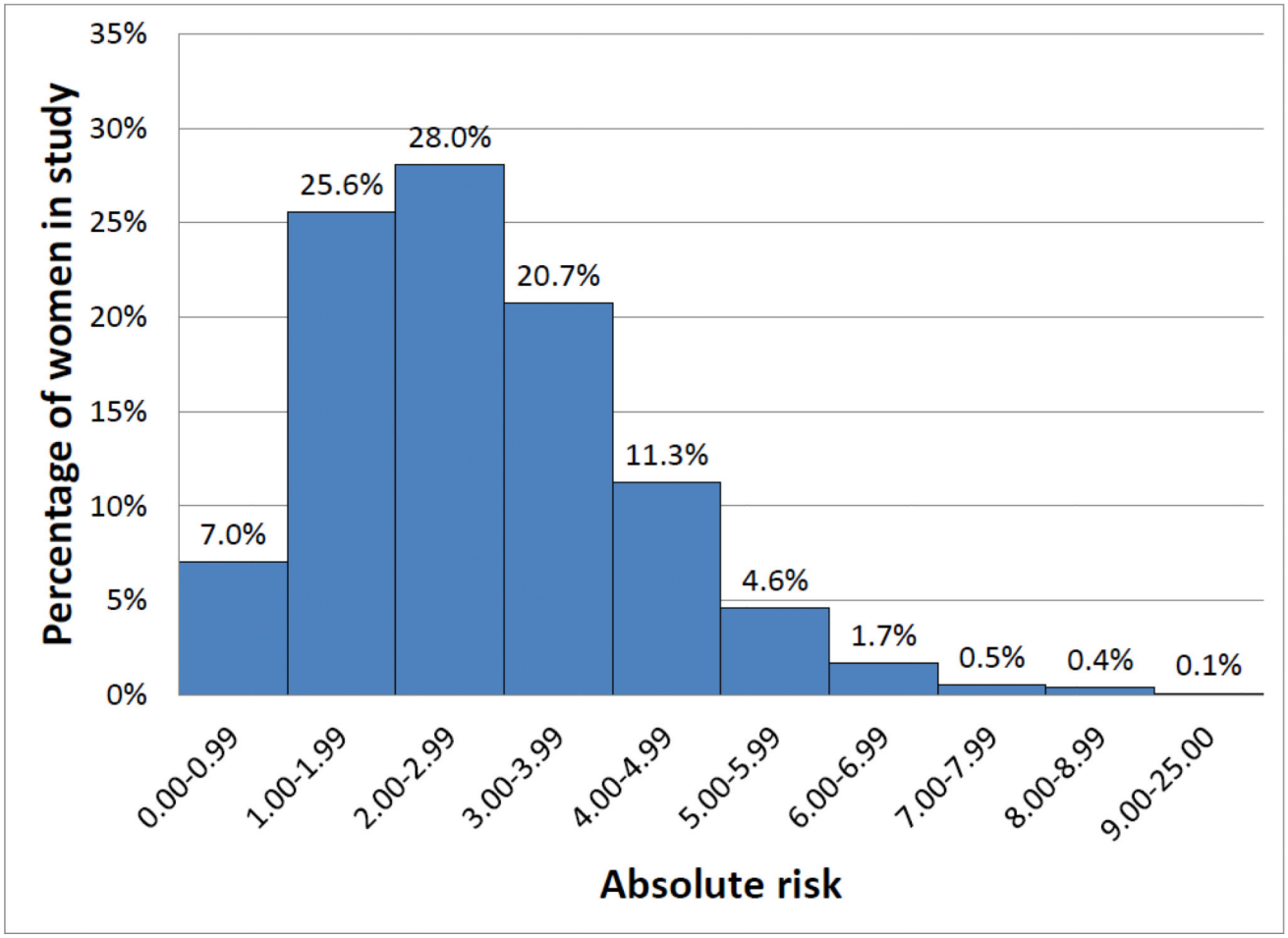

Figure 2.

a–2d. Distribution of 5-year and 10-year risk for women with the one-measure (2a and 2b) and two-measure density models (2c and 2d).

Table 1

Baseline characteristics of the study cohort

	No breast cancer		Breast cancer	
Risk factor	**N**	**(%)**	**N**	**(%)**
Total	708,939		13,715	
Age group, years				
35–39	17,925	2.5	209	1.5
40–44	133,450	18.8	1,616	11.8
45–49	131,099	18.5	1,996	14.6
50–54	133,663	18.9	2,454	17.9
55–59	100,579	14.2	2,313	16.9
60–64	76,805	10.8	1,914	14.0
65–69	64,297	9.1	1,687	12.3
70–74	51,121	7.2	1,526	11.1
Race/Ethnicity				
White, non-Hispanic	559,249	78.9	11,545	84.2
Black, non-Hispanic	48,341	6.8	839	6.1
Asian, Native Hawaiian, or Pacific Islander	30,707	4.3	366	2.7
American Indian or Alaska Native	4,665	0.7	47	0.3
Hispanic	56,646	8.0	752	5.5
Other, Mixed (2+ races)	9,331	1.3	166	1.2
First-degree relatives with breast cancer				
No	613,430	86.5	10,955	79.9
Yes	95,509	13.5	2,760	20.1
History of breast biopsy				
No	569,770	80.4	9,910	72.3
Yes	139,169	19.6	3,805	27.7
BI-RADS breast density stratified by most recent and previous measure				
Most recent density = a	55,251	7.8	519	3.8
a:a	28,329	4.0	235	1.7
b:a	24,146	3.4	249	1.8
c:a	2,498	0.4	29	0.2
d:a	278	0.04	6	0.04
Most recent density = b	303,167	42.8	5,275	38.5
a:b	24,826	3.5	292	2.1
b:b	202,947	28.6	3,445	25.1
c:b	71,146	10.0	1,431	10.4
d:b	4,248	0.6	107	0.8
Most recent density = c	286,402	40.4	6,414	46.8
a:c	2,728	0.4	46	0.3
b:c	70,299	9.9	1,443	10.5
c:c	183,857	25.9	4,177	30.5

	No breast cancer		Breast cancer	
Risk factor	**N**	**(%)**	**N**	**(%)**
d:c	29,518	4.2	748	5.5
Most recent density = d	64,119	9.0	1,507	11.0
a:d	210	0.03	3	0.02
b:d	3,501	0.5	83	0.6
c:d	25,645	3.6	614	4.5
d:d	34,763	4.9	807	5.9
Mean time between examinations; years		1.82		1.83

BI-RADS: Breast Imaging Reporting and Data System density measure; a= almost entirely fat; b=scattered fibroglandular densities; c=heterogeneously dense; d=extremely dense.

Table 2

Association between most recent BI-RADS breast density, most recent and previous BI-RADS density, and breast cancer risk factors and breast cancer risk for woman age 50 years at study entry

	Hazard ratio for women age 50 (95% CI)
BI-RADS breast density, most recent measure[a]	
a: Almost entirely fat	0.47 (0.41, 0.55)
b: Scattered fibroglandular densities	referent
c: Heterogeneously dense	1.52 (1.45, 1.59)
d: Extremely dense	1.82 (1.71, 1.94)
First-degree relatives with breast cancer[a]	
No	referent
Yes	1.59 (1.50, 1.68)
History of breast biopsy[a]	
No	referent
Yes	1.36 (1.31, 1.41)
BI-RADS breast density, stratified by most recent and previous measure[b]	
Most recent density = a	
a:a	0.41 (0.32, 0.52)
b:a	0.56 (0.46, 0.69)
c:a	0.71 (0.42, 1.21)
d:a	1.64 (0.73, 3.69)
Most recent density = b	
a:b	0.57 (0.46, 0.70)
b:b	referent
c:b	1.38 (1.27, 1.49)
d:b	1.96 (1.59, 2.41)
Most recent density = c	
a:c	0.87 (0.54, 1.38)
b:c	1.36 (1.26, 1.48)
c:c	1.71 (1.61, 1.82)
d:c	1.97 (1.80, 2.15)
Most recent density = d	
a:d	1.32 (0.39, 4.49)
b:d	1.99 (1.59, 2.50)
c:d	1.97 (1.80, 2.17)
d:d	2.00 (1.84, 2.18)

BI-RADS: Breast Imaging Reporting and Data System density measure; a= almost entirely fat; b=scattered fibroglandular densities; c=heterogeneously dense; d=extremely dense.

[a] Adjusted for age at entry (linear and quadratic terms) and race/ethnicity, with interactions between most recent BI-RADS density and age at entry (linear), first-degree relatives and age at entry (linear and quadratic), and race/ethnicity and age at entry (linear).

[b] Adjusted for age at entry (linear and quadratic terms) and race/ethnicity, with interactions between most recent and previous BI-RADS density and age at entry (linear), first-degree relatives and age at entry (linear and quadratic), and race/ethnicity and age at entry (linear).

Table 3

Calibration of the BCSC Two-measure Density Model in risk factor subgroups

		5-year risk model			10-year risk model		
Risk group	**Number of women**	**Observed 5-year rate[a]**	**Expected 5-year rate[b]**	**E/O[c] (95% CI)**	**Observed 10-year rate[a]**	**Expected 10-year rate[b]**	**E/O[c] (95% CI)**
Full cohort	722,654	1.34	1.31	0.98 (0.96, 1.00)	2.95	2.80	0.95 (0.94, 0.96)
Age group, years							
35–39	18,134	0.72	0.51	0.71 (0.60, 0.84)	2.03	1.34	0.66 (0.60, 0.73)
40–44	135,066	0.88	0.68	0.77 (0.73, 0.82)	2.07	1.65	0.80 (0.77, 0.83)
45–49	133,095	1.05	0.99	0.94 (0.89, 0.99)	2.33	2.27	0.97 (0.94, 1.01)
50–54	136,117	1.21	1.28	1.06 (1.01, 1.11)	2.77	2.82	1.02 (0.99, 1.05)
55–59	102,892	1.59	1.54	0.97 (0.92, 1.02)	3.47	3.27	0.94 (0.91, 0.97)
60–64	78,719	1.73	1.79	1.03 (0.98, 1.09)	3.71	3.65	0.98 (0.95, 1.02)
65–69	65,984	1.83	1.98	1.08 (1.02, 1.14)	3.79	3.90	1.03 (0.99, 1.07)
70–74	52,647	2.04	2.10	1.03 (0.97, 1.09)	4.15	3.95	0.95 (0.91, 0.99)
Race/Ethnicity							
White, non-Hispanic	570,794	1.40	1.38	0.99 (0.96, 1.01)	3.02	2.94	0.97 (0.96, 0.99)
Black, non-Hispanic	49,180	1.14	1.21	1.06 (0.98, 1.15)	2.82	2.56	0.91 (0.86, 0.96)
Asian, Native Hawaiian, or	31,073	1.13	0.99	0.88 (0.79, 0.97)	2.68	2.08	0.78 (0.73, 0.83)
American Indian or Alaska	4,712	0.83	1.02	1.23 (0.90, 1.68)	1.65	2.14	1.30 (1.04, 1.62)
Hispanic	57,398	1.00	0.96	0.96 (0.88, 1.04)	2.47	2.05	0.83 (0.79, 0.87)
Other, Mixed (2+ races)	9,497	1.48	1.26	0.85 (0.72, 1.00)	2.98	2.74	0.92 (0.82, 1.03)
BI-RADS breast density stratified by most recent and previous measure							
Most recent density = a							
a:a	28,564	0.56	0.63	1.13 (0.96, 1.31)	1.44	1.28	0.89 (0.81, 0.98)
b:a	24,395	0.74	0.77	1.04 (0.90, 1.20)	1.68	1.59	0.95 (0.86, 1.04)
c:a	2,527	0.75	0.89	1.19 (0.76, 1.86)	2.20	1.85	0.84 (0.65, 1.09)
d:a	284	1.50	1.31	0.87 (0.34, 2.26)	2.65	2.98	1.12 (0.55, 2.30)
Most recent density = b							
a:b	25,118	0.85	0.83	0.98 (0.85, 1.12)	1.75	1.69	0.97 (0.88, 1.06)
b:b	206,392	1.16	1.17	1.01 (0.97, 1.05)	2.53	2.43	0.96 (0.93, 0.99)

Risk group	Number of women	5-year risk model: Observed 5-year rate[a]	5-year risk model: Expected 5-year rate[b]	5-year risk model: E/O[c] (95% CI)	10-year risk model: Observed 10-year rate[a]	10-year risk model: Expected 10-year rate[b]	10-year risk model: E/O[c] (95% CI)
c:b	72,577	1.35	1.38	1.02 (0.96, 1.09)	3.11	2.92	0.94 (0.90, 0.98)
d:b	4,355	1.77	1.64	0.93 (0.74, 1.16)	3.95	3.59	0.91 (0.78, 1.06)
Most recent density = c							
a:c	2,774	1.14	1.20	1.05 (0.74, 1.49)	2.52	2.45	0.97 (0.77, 1.23)
b:c	71,742	1.38	1.34	0.97 (0.91, 1.03)	2.97	2.85	0.96 (0.92, 1.00)
c:c	188,034	1.60	1.53	0.96 (0.92, 0.99)	3.51	3.31	0.94 (0.92, 0.97)
d:c	30,266	1.75	1.64	0.94 (0.86, 1.02)	3.82	3.60	0.94 (0.89, 1.00)
Most recent density = d							
a:d	213	0	1.08		2.56	2.33	0.91 (0.39, 2.11)
b:d	3,584	1.55	1.57	1.01 (0.78, 1.32)	3.87	3.46	0.89 (0.76, 1.06)
c:d	26,259	1.72	1.60	0.93 (0.85, 1.02)	3.80	3.53	0.93 (0.87, 0.99)
d:d	35,570	1.69	1.51	0.89 (0.82, 3.64)	3.64	3.38	0.93 (0.88, 0.98)
First-degree relatives with							
No	624,385	1.23	1.21	0.98 (0.96, 1.01)	2.74	2.58	0.94 (0.93, 0.96)
Yes	98,269	2.05	1.96	0.96 (0.92, 1.00)	4.28	4.18	0.98 (0.95, 1.01)
History of breast biopsy							
No	579,680	1.21	1.17	0.97 (0.94, 0.99)	2.67	2.51	0.94 (0.93, 0.96)
Yes	142,974	1.88	1.88	1.00 (0.96, 1.04)	4.07	3.98	0.98 (0.95, 1.00)

BI-RADS: Breast Imaging Reporting and Data System density measure; a= almost entirely fat; b=scattered fibroglandular densities; c=heterogeneously dense; d=extremely dense.

[a] The observed 5-year rate uses the Kaplan-Meier estimator to estimate the number of cancers within each subgroup.

[b] The expected rate is the average of the BCSC Two-measure Density Model predicted risk for each woman in the subgroup. No additional adjustments were performed.

[c] E/O: Expected rate divided by the observed rate.

Table 4

Predicted five-year risk of invasive breast cancer by most recent and previous BI-RADS breast density measures and by risk factor subgroups

			5-year risk[a] No family history		5-year risk[a] Family history	
Breast density group	**Number of women**	**5-year risk of breast cancera (95% CI)**	**No biopsy**	**Biopsy**	**No biopsy**	**Biopsy**
Most recent density = a	55,770	0.71 (0.64, 0.78)	0.62	0.93	0.98	1.46
a:a	28,564	0.63 (0.54, 0.72)	0.55	0.81	0.87	1.26
b:a	24,395	0.77 (0.66, 0.88)	0.67	1.00	1.06	1.57
c:a	2,527	0.89 (0.52, 1.26)	0.75	1.26	1.19	**1.84**
d:a	284	1.31 (NE)	1.09	1.49	**1.76**	**1.96**
Most recent density = b	308,442	1.21 (1.17, 1.25)	1.02	1.57	1.62	2.44
a:b	25,118	0.83 (0.72, 0.94)	0.72	1.08	1.16	1.71
b:b	206,392	1.17 (1.12, 1.22)	0.99	1.51	1.57	2.35
c:b	72,577	1.38 (1.29, 1.46)	1.15	**1.79**	**1.83**	2.75
d:b	4,355	1.64 (1.26, 2.02)	1.39	**2.07**	**2.23**	3.06
Most recent density = c	292,816	1.50 (1.46, 1.54)	1.24	1.93	1.96	3.01
a:c	2,774	1.20 (0.79, 1.60)	1.03	*1.54*	*1.60*	2.35
b:c	71,742	1.34 (1.26, 1.43)	1.12	1.73	1.78	2.67
c:c	188,034	1.53 (1.48, 1.59)	1.27	1.96	2.00	3.05
d:c	30,266	1.64 (1.49, 1.78)	1.34	2.05	2.10	3.24
Most recent density = d	65,626	1.56 (1.46, 1.66)	1.28	1.93	2.02	3.04
a:d	213	1.08 (NE)	0.95	*1.16*	*1.65*	2.10
b:d	3,584	1.57 (1.16, 1.98)	1.33	1.90	2.10	3.00
c:d	26,259	1.60 (1.45, 1.75)	1.31	2.00	2.08	3.10
d:d	35,570	1.51 (1.38, 1.63)	1.24	1.82	1.96	2.90

BI-RADS: Breast Imaging Reporting and Data System density measure; a= almost entirely fat; b=scattered fibroglandular densities; c=heterogeneously dense; d=extremely dense). Bold numbers are women who had an increase in 5-year risk from <1.67% with the one-density model to ≥1.67% with the two-density model. Italicized numbers are women who had a decrease in 5-year risk from ≥1.67% with the one-density model to <1.67% with the two-density model.
NE = Not estimable (number of expected cancers < 5)

[a]5-year risk estimates for Most recent density = a; Most recent density = b; Most recent density = c; and Most recent density = d are calculated as the mean predicted risk from the absolute risk model with most recent BI-RADS density. 5-year risk estimates for combinations of most recent and previous density are calculated as the mean predicted risk from the absolute risk model with most recent and previous BI-RADS density.