Published OnlineFirst March 19, 2013; DOI: 10.1158/1055-9965.EPI-12-1208-T

Cancer Epidemiology, Biomarkers & Prevention

Research Article

Risk Factors for Second Screen-Detected or Interval Breast Cancers in Women with a Personal History of Breast Cancer Participating in Mammography Screening

Nehmat Houssami[1], Linn A. Abraham[2], Karla Kerlikowske[3,4], Diana S.M. Buist[2,5], Les Irwig[1], Janie Lee[6], and Diana L. Miglioretti[2,7]

Abstract

Background: Women with a personal history of breast cancer (PHBC) have increased risk of an interval cancer. We aimed to identify risk factors for second (ipsilateral or contralateral) screen-detected or interval breast cancer within 1 year of screening in PHBC women.

Methods: Screening mammograms from women with history of early-stage breast cancer at Breast Cancer Surveillance Consortium-affiliated facilities (1996–2008) were examined. Associations between woman-level, screen-level, and first cancer variables and the probability of a second breast cancer were modeled using multinomial logistic regression for three outcomes [screen-detected invasive breast cancer, interval invasive breast cancer, or ductal carcinoma in situ (DCIS)] relative to no second breast cancer.

Results: There were 697 second breast cancers, of these 240 were interval cancers, among 67,819 screens in 20,941 women. In separate models for women with DCIS *or* invasive first cancer, first breast cancer surgery predicted all three second breast cancer outcomes ($P < 0.001$), and high ORs for second breast cancers (between 1.95 and 4.82) were estimated for breast conservation *without* radiation (relative to mastectomy). In women with invasive first breast cancer, additional variables predicted risk ($P < 0.05$) for at least one of the three outcomes: first-degree family history, dense breasts, longer time between mammograms, young age at first breast cancer, first breast cancer stage, and adjuvant systemic therapy for first breast cancer; and risk of interval invasive breast cancer was highest in women <40 years at first breast cancer (OR, 3.41; 1.34–8.70), those with extremely dense breasts (OR, 2.55; 1.4–4.67), and those treated with breast conservation without radiation (OR, 2.67; 1.53–4.65).

Conclusion: Although the risk of a second breast cancer is modest, our models identify risk factors for interval second breast cancer in PHBC women.

Impact: Our findings may guide discussion and evaluations of tailored breast screening in PHBC women, and incorporating this information into clinical decision-making warrants further research. *Cancer Epidemiol Biomarkers Prev; 22(5); 946–61. ©2013 AACR.*

Introduction

Early detection of second breast cancers, ipsilateral in-*breast* recurrence or new cancer, or contralateral cancer, in women with a personal history of breast cancer (PHBC) is considered beneficial (1–4). Annual screening or surveillance mammography (referred to as "screening") is therefore recommended in women with a PHBC in most guidelines and consensus recommendations (5–9). Some experts and guidelines also recommend adjunct screening (MRI or ultrasound) in PHBC women who have additional risk factors (6, 10–12). Recent research from the Breast Cancer Surveillance Consortium (BCSC) (13) has shown that women with a history of early-stage breast cancer (BC) have higher underlying cancer rates and higher interval cancer rates than age and breast density–matched screening participants without a PHBC (13). This work provided evidence that screening mammography in PHBC women had lower sensitivity relative to that in

Authors' Affiliations: [1]Screening and Test Evaluation Program, School of Public Health, Sydney Medical School, University of Sydney, Sydney, Australia; [2]Group Health Research Institute, Group Health Cooperative, Seattle, Washington; [3]Departments of Medicine and Epidemiology and Biostatistics, University of California, San Francisco, California; [4]General Internal Medicine Section, Department of Veterans Affairs, University of California, San Francisco, California; [5]Departments of Epidemiology and Health Services, University of Washington, Seattle, Washington; [6]Institute for Technology Assessment, Department of Radiology, Massachusetts General Hospital, Boston, Massachusetts; and [7]Division of Biostatistics, Department of Public Health Sciences, University of California, Davis, Washington

Note: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the NIH.

Corresponding Author: Nehmat Houssami, Screening and Test Evaluation Program, School of Public Health (A27), Sydney Medical School, University of Sydney, NSW 2006, Australia. Phone: 610-419273510; Fax: 610-297-051046; E-mail: nehmath@med.usyd.edu.au

doi: 10.1158/1055-9965.EPI-12-1208-T

Published OnlineFirst March 19, 2013; DOI: 10.1158/1055-9965.EPI-12-1208-T

women without PHBC, although the lower relative sensitivity of mammography (but similar proportion of early-stage disease) may be partly due to greater breast awareness and early reporting of symptoms or more intensive clinical and imaging surveillance in PHBC women (13).

In our previous work, we focused on estimating screening accuracy and interval cancer rates and also described factors associated with cancer rates in PHBC women based on separate analysis of each variable (13) but we did not investigate risk in multivariable models. In the present study, we aimed to identify risk factors that independently determine the risk of a second breast cancer. Risk factor models for breast cancer have been developed for women at average population risk (14–16) as well as those with increased risk due to cancer susceptibility gene mutations or family history of breast cancer (17, 18). Five-year risk for second breast cancer has been reported in PHBC women (19) and one study has estimated sufficiently high risk to support MRI screening recommendations in PHBC women (12). However, there are no comprehensive studies reporting risk factors for a second breast cancer that elucidate interval cancer risk factors in PHBC women participating in mammography screening. Because second breast cancer risk is influenced by tumor characteristics and treatment of the first cancer (13, 19) and possibly by underlying host factors such as obesity, and because screening outcomes in PHBC women differ from those in population screening (13), identifying risk factors for second breast cancer would help clinicians identify PHBC women at increased risk of a screen-detected or interval second cancer and may guide decisions on tailored screening. This may be particularly relevant given that our earlier work showed that interval cancers were twice as likely to be stage IIB or a higher stage or to be node-positive than screen-detected breast cancer in PHBC women (13, 19) and therefore interval cancers may be associated with different outcomes.

We aimed to develop multivariable models that identify independent risk factors for a second (ipsilateral or contralateral) breast cancer within 1 year of screening mammography in women with a PHBC. We examined the risk of the second breast cancer being screen-detected or an interval cancer in a cohort of women with PHBC who participated in mammography through BCSC-affiliated facilities (13).

Materials and Methods

We included screening mammograms from women with a PHBC who received screening between 1996 and 2008 (13) at facilities affiliated with 5 BCSC registries: Carolina Mammography Registry (North Carolina), Group Health Registry (Washington State), New Hampshire Mammography Network, New Mexico Mammography Project, and Vermont Breast Cancer Surveillance System. These registries collect demographic and mammography information linked with state or Surveillance Epidemiology and End Results (SEER) cancer registries and pathology databases to ascertain breast cancer diagnoses including recurrences. Each registry and BCSC Statistical Coordinating Center (SCC) received Institutional Review Board approval for active or passive consenting processes or consent waiver to enroll women, link data, and conduct analytic studies. All procedures are Health Insurance Portability and Accountability Act compliant and all registries and SCC received a Federal Certificate of Confidentiality and other protections for identities of women, physicians, and facilities who are subjects of this research.

Eligible screening mammograms were from women with an initial early-stage breast cancer (13), including ductal carcinoma *in-situ* (DCIS) or stage I–II invasive carcinoma—this cohort has been well-characterized (13); the present study had a slightly longer timeframe and included 1,863 more PHBC women than the previously evaluated cohort. Cancer registry and pathology databases were used to ascertain whether a woman had a subsequent breast cancer diagnosis, diagnosis date, and cancer characteristics. Our definition of a screening mammogram was described in earlier work (13, 19) and included mammograms indicated to be a routine screen (by radiologist or technologist) and excluded screens from women who reported symptoms. A positive mammogram was based on the final imaging assessment and included BI-RADS assessments of 4 or 5, or 0 or 3 with recommendation for biopsy, fine-needle aspiration, or surgical consultation (13, 20).

Demographic and mammogram characteristics

Age, self-reported race/ethnicity, first-degree family history of breast cancer, menopausal status, time since last mammogram (before the screening mammogram included in the analysis), and history of breast plastic surgery were collected at the time of screening. Breast density and type of mammogram (film or digital) were routinely recorded.

First cancer characteristics and follow-up for second breast cancers

Time since first cancer was the difference between the screening mammogram date and the date of first breast cancer diagnosis (13). For first cancer, type (DCIS, stage I or II invasive), radiation therapy, adjuvant systemic therapy, and primary surgery (breast conservation, mastectomy) were based on records from cancer registry and pathology databases that include treatments received within 6 months of initial diagnosis. For missing cancer registry surgery information, self-reported mastectomy and lumpectomy history (collected within 18 months after diagnosis and before second breast cancer diagnosis) was used. Screening mammograms were considered to be associated with an outcome of a second breast cancer (in-breast recurrence or second ipsilateral or contralateral breast cancer) if DCIS or invasive breast cancer were observed within 1 year of that screen or before the next screen if it occurred within 9 to 12 months after the screen.

Published OnlineFirst March 19, 2013; DOI: 10.1158/1055-9965.EPI-12-1208-T

If a second breast cancer outcome was observed during follow-up after a negative mammogram, this was considered a false-negative screen and defined an interval (second) breast cancer.

Statistical analysis

Frequency distributions of screens and cancers were computed for demographic, mammogram, and first cancer characteristics. Cancer rates per 1,000 screens and 95% confidence intervals (CI) were calculated. Using multinomial logistic regression, we examined the association between each variable and the probability (OR) of a second breast cancer using joint modeling for three outcomes (screen-detected invasive breast cancer, interval invasive breast cancer, or DCIS) whereby the OR for each outcome was estimated relative to that of not having a second breast cancer (referent). Because the majority of DCIS (second cancer) in our cohort was screen-detected, DCIS was considered as a single outcome in these models. Univariate analyses were conducted separately in PHBC women with DCIS first cancer and those with invasive first cancer given that some variables (e.g., node status, chemotherapy) do not apply to, or would be infrequently reported in, those with DCIS history: variables found to be associated with breast cancer risk (based on global $P < 0.05$ for joint modeling for 3 outcomes) in univariate models were entered into a multivariable model for each group defined by first breast cancer type; breast density and body mass index (BMI) were also included on the basis of prior knowledge of their association with second breast cancer risk (13, 21–23).

Missing data were imputed for the final multivariable models using a chained equations method (24, 25). This method imputed each missing variable using a regression model conditional on all the other variables in the model; this was repeated for all variables missing data. Ten imputations were conducted in STATA 12.0. For variables shown to be significantly associated with outcomes in each final model, we tested for differences in the estimated odds of an interval compared with screen-detected invasive breast cancer, relative to no second breast cancer during follow-up.

To evaluate model fit, receiver operating characteristic (ROC) curves and areas under the curves (AUC) were computed on the basis of logistic regression models that were conducted for each outcome (screen-detected or interval invasive breast cancer or DCIS) relative to no second cancer. AUCs were averaged over the 10 imputations to obtain an overall AUC. The AUCs and SEs were combined across imputations to compute a 95% CI for the AUC (26). We did not account for correlation due to multiple screens on the same women because we modeled the probability of a second breast cancer diagnosis within 1 year of mammography. Thus, women only contributed observations up until the time they were diagnosed with a second breast cancer. In this case, the joint likelihood of the multiple outcomes for a woman is proportional to the multinomial likelihood that considers all outcomes for a woman to be independent events (27).

Results

There were 67,819 screening mammograms from 20,941 women with PHBC: 697 cancers (520 invasive breast cancer and 177 DCIS) occurred within 12 months of screening; of these, 240 were interval cancers (206 invasive breast cancer and 34 DCIS). Cancer rates per 1,000 screens (95% CI) were: overall cancer rates 10.3 per 1,000 (9.5–11.1), invasive breast cancer 7.7 per 1,000 (7.0–8.4), DCIS 2.6 per 1,000 (2.2–3.0), interval breast cancer 3.5 per 1,000 (3.1–4.0), and interval invasive breast cancer 3.0 per 1,000 (2.6–3.5). Table 1 shows the distribution of variables for all screens and overall and variable-specific cancer rates.

Table 2 reports univariate analyses of variable-specific ORs for the (second) cancer outcomes relative to no second breast cancer, among women with DCIS first cancer. Significant variables were age at mammography, first-degree family history of breast cancer, menopausal status, primary surgery, and adjuvant systemic therapy. Table 3 reports univariate models of variable-specific ORs for the cancer outcomes among women with invasive first breast cancer. Significant variables were age at mammography, first-degree family history of breast cancer, menopausal status, breast density, time since last mammogram, time since first breast cancer, first cancer mode of detection, age at first breast cancer, stage of first breast cancer, primary surgery, and adjuvant systemic therapy. Significant variables were carried forward into multivariable models, with the exception of the 2 (correlated) age variables for which only age at first breast cancer was considered. For women with an invasive first breast cancer, first cancer mode of detection was not included in the final model due to high numbers of screens missing these data.

The multivariable model results for women with DCIS first cancer is shown in Table 4: first breast cancer surgical treatment (with/without radiation) was associated with all 3 outcomes ($P < 0.001$). The highest odds of all outcomes were for screens of women who had breast conservation without radiation. Other significant associations noted only for specific outcomes (shown in bold font in tables) were increased risk in screens of women aged 70–79 (relative to 60–69 year age group) for screen-detected invasive breast cancer (OR, 2.14) or interval invasive breast cancer (OR, 3.06), and BMI was associated with increased risk of screen-detected invasive second breast cancer (OR, 2.32 and 2.96 for screens in women with increasing obesity categories). In this model, there was no evidence that the odds of an interval versus screen-detected invasive breast cancer significantly differed. The estimated AUCs (95% CIs) for screen-detected invasive breast cancer, interval invasive breast cancer, and DCIS (vs. no second BC) were 0.72 (0.67–0.77), 0.71 (0.63–0.78), and 0.71 (0.64–0.78), respectively.

The multivariable model in women with invasive first cancer, shown in Table 5, indicates that several variables

Published OnlineFirst March 19, 2013; DOI: 10.1158/1055-9965.EPI-12-1208-T

remained significantly associated with outcomes: first-degree family history of breast cancer ($P = 0.021$), breast density ($P = 0.016$), time since last mammogram ($P = 0.048$), age at first breast cancer ($P = 0.023$), stage of first breast cancer ($P = 0.032$), primary surgery ($P < 0.001$), and adjuvant systemic therapy ($P = 0.019$). Relative to screens in women who had mastectomy for first breast cancer, screens in those who had breast conservation had increased odds of screen-detected or interval invasive breast cancer or DCIS, with the highest ORs estimated in women who had breast conservation without radiation. Receipt of endocrine therapy reduced the OR for screen-detected invasive breast cancer and for DCIS. Age < 40 years at first breast cancer, breast density (BI-RADS "extremely dense"), and first-degree family history of breast cancer significantly increased the odds of an *interval* invasive breast cancer (Table 5). Time since last mammogram (15+ months) increased the odds of screen-detected invasive breast cancer (OR, 1.59); first cancer stage (IIB) increased the odds of DCIS (OR, 2.46). Although time since the first breast cancer was weakly associated with outcomes in the multivariable model ($P = 0.06$), screens in women with ≥ 7 years (referent 1–2 years) from first breast cancer had higher odds of screen-detected invasive breast cancer or DCIS. In this model, the odds of an interval invasive breast cancer was significantly higher than the odds of screen-detected invasive breast cancer ($P = 0.035$), relative to no second breast cancer, in women with extremely dense breasts. There was no evidence that the odds of an interval versus screen-detected invasive breast cancer, relative to no second breast cancer, significantly differed for any other significant risk factor.

Further examination of the multivariable model in women with invasive first cancer that varied the referent age group or density categories (not shown in Table 5) consistently showed that age < 40 years at first breast cancer diagnosis was significantly associated with risk of an interval invasive breast cancer relative to other age groups with ORs ranging between 3.13 (1.18–8.28) and 4.68 (1.30–16.89). Relative to screens classified as BI-RADS extremely dense, those with fatty breasts were at significantly lower risk of an interval invasive BC (OR, 0.17; 0.04–0.69) and of DCIS (OR, 0.26; 0.07–0.97), and those with scattered fibroglandular tissue also had lower risk of an interval invasive BC (OR, 0.39; 0.21–0.72). On the basis of the final model for women with invasive first cancer (Table 5), estimated AUCs (95% CIs) for screen-detected invasive breast cancer, interval invasive breast cancer, and DCIS were 0.67 (0.63–0.70), 0.70 (0.65–0.75), and 0.73 (0.68–0.78), respectively.

Discussion

We present models that identify risk factors for a second breast cancer (ipsilateral breast recurrence or second cancer in either breast) in PHBC women who participated in mammography screening and report risk factors for interval invasive breast cancer. Our previous investigation of this cohort showed that interval cancers were more frequent among women with a PHBC (that may be partly due to greater breast awareness and early reporting of symptoms, or more intensive clinical and imaging surveillance) relative to those without PHBC (13), highlighting the need to identify risk factors for interval breast cancer in mammography screening of PHBC women. In the present study of 67,819 screening mammograms from PHBC women, we observed an overall cancer rate of 10.3 per 1,000 screens within one year of screening, with an invasive breast cancer rate of 7.7 per 1,000 screens. The interval invasive breast cancer rate was 3.0 per 1,000 screens within 1 year of mammography showing that PHBC women are at increased risk of an interval invasive breast cancer.

Our multivariable models make a new contribution to existing knowledge on the risk of second breast cancer by highlighting factors that predict the likelihood of a screen-detected invasive *or* an interval invasive (second) breast cancer *or* DCIS within 1 year of receiving screening mammography. Distinction between these 3 outcomes is relevant for follow-up care of PHBC women in whom risk factors for second breast cancers have been reported by other researchers and notably work from the BCSC (19); hence, our research has uniquely focused on risk factors for interval as opposed to screen-detected second breast cancer because factors increasing the risk of screen-detected second breast cancer are effectively "managed" through mammography screening. Our work, therefore, addresses the gap in knowledge about risk factors that render mammography screening less sensitive in PHBC women and increase the odds of an interval invasive breast cancer among screened women. Furthermore, most studies reporting on second breast cancers in the context of PHBC women participating in screening (2–4, 11, 28) have considered either ipsilateral *or* contralateral second breast cancer (and not both), have not estimated interval cancer rates or risk of interval second breast cancer, have not examined a broad range of potentially associated variables (2–4, 11, 28), or have not reported multivariable models (13). The work of Buist and colleagues (19) is the only study to have examined second breast cancer risk in PHBC women participating in screening using multivariable analysis; however, it considered overall risk of a second breast cancer, whereas we specifically examined the 3 defined second breast cancer outcomes. Although variables increasing the overall risk of a second breast cancer would be expected to increase the risk of screen-detected or interval second breast cancer, for the reasons outlined above, we aimed to address the evidence-gap on risk factors for interval second breast cancer.

In women with DCIS first cancer (Table 4), the dominant factor driving risk of another breast cancer was surgical treatment (with/without radiation) received for first breast cancer, which was significantly associated with all modeled outcomes. Although the risk of another breast cancer depends on the number of

Published OnlineFirst March 19, 2013; DOI: 10.1158/1055-9965.EPI-12-1208-T

Table 1. Distribution of variables, number of cancers, and cancer rates in women with a PHBC who participated in mammography screening (BCSC 1996–2008)

Variable (proportion missing data for variable where applicable)	Number of screening mammograms (%)	Number of second cancers (number invasive cancers)	Number of interval cancers (number invasive)	Cancer rate per 1,000 screens (95% CI)	Invasive cancer rate per 1,000 screens (95% CI)	Interval cancer rate per 1,000 screens (95% CI)	Invasive interval cancer rate per 1,000 screens (95% CI)
All screening mammograms	**67,819**	**697 (520)**	**240 (206)**	**10.3 (9.5–11.1)**	**7.7 (7.0–8.4)**	**3.5 (3.1–4.0)**	**3.0 (2.6–3.5)**
Age at mammography, y							
< 40	815 (1.2)	15 (13)	11 (10)	18.4 (10.3–30.2)	16.0 (8.5–27.1)	13.5 (6.8–24.0)	12.3 (5.9–22.4)
40–49	6,925 (10.2)	99 (72)	46 (39)	14.3 (11.6–17.4)	10.4 (8.1–13.1)	6.6 (4.9–8.9)	5.6 (4.0–7.7)
50–59	16,998 (25.1)	169 (118)	61 (52)	9.9 (8.5–11.6)	6.9 (5.7–8.3)	3.6 (2.7–4.6)	3.1 (2.3–4)
60–69	17,326 (25.5)	157 (112)	39 (33)	9.1 (7.7–10.6)	6.5 (5.3–7.8)	2.3 (1.6–3.1)	1.9 (1.3–2.7)
70–79	17,195 (25.4)	173 (142)	61 (56)	10.1 (8.6–11.7)	8.3 (7.0–9.7)	3.5 (2.7–4.6)	3.3 (2.5–4.2)
80+	8,560 (12.6)	84 (63)	22 (16)	9.8 (7.8–12.1)	7.4 (5.7–9.4)	2.6 (1.6–3.9)	1.9 (1.1–3.0)
Race/ethnicity (3.8%)							
White, non-Hispanic	55,444 (85.0)	569 (421)	187 (158)	10.3 (9.4–11.1)	7.6 (6.9–8.4)	3.4 (2.9–3.9)	2.8 (2.4–3.3)
Black, non-Hispanic	2,370 (3.6)	25 (20)	10 (9)	10.5 (6.8–15.5)	8.4 (5.2–13.0)	4.2 (2.0–7.7)	3.8 (1.7–7.2)
Hispanic	4,820 (7.4)	43 (33)	19 (18)	8.9 (6.5–12.0)	6.8 (4.7–9.6)	3.9 (2.4–6.1)	3.7 (2.2–5.9)
Asian, Pacific Islander	1,206 (1.8)	14 (9)	4 (4)	11.6 (6.4–19.4)	7.5 (3.4–14.1)	3.3 (0.9–8.5)	3.3 (0.9–8.5)
Other	1,388 (2.1)	13 (9)	5 (3)	9.4 (5.0–16.0)	6.5 (3.0–12.3)	3.6 (1.2–8.4)	2.2 (0.4–6.3)
First-degree family history of breast cancer (15.9%)							
No	43,597 (76.5)	404 (296)	144 (123)	9.3 (8.4–10.2)	6.8 (6.0–7.6)	3.3 (2.8–3.9)	2.8 (2.3–3.4)
Yes	13,409 (23.5)	176 (132)	60 (54)	13.1 (11.3–15.2)	9.8 (8.2–11.7)	4.5 (3.4–5.8)	4.0 (3.0–5.3)
Menopausal status (12.4%)							
Pre	4,054 (6.8)	74 (47)	34 (28)	18.3 (14.4–22.9)	11.6 (8.5–15.4)	8.4 (5.8–11.7)	6.9 (4.6–10.0)
Peri	898 (1.5)	16 (12)	4 (4)	17.8 (10.2–28.8)	13.4 (6.9–23.2)	4.5 (1.2–11.4)	4.5 (1.2–11.4)
Post	54,471 (91.7)	518 (393)	162 (140)	9.5 (8.7–10.4)	7.2 (6.5–8.0)	3.0 (2.5–3.5)	2.6 (2.2–3.0)
BI-RADS breast density (20.3%)							
1—almost entirely fatty	4,104 (7.6)	20 (16)	5 (5)	4.9 (3.0–7.5)	3.9 (2.2–6.3)	1.2 (0.4–2.8)	1.2 (0.4–2.8)
2—scattered fibroglandular tissue	25,806 (47.7)	232 (178)	72 (63)	9.0 (7.9–10.2)	6.9 (5.9–8.0)	2.8 (2.2–3.5)	2.4 (1.9–3.1)
3—heterogeneously dense	21,221 (39.3)	238 (174)	87 (72)	11.2 (9.8–12.7)	8.2 (7.0–9.5)	4.1 (3.3–5.1)	3.4 (2.7–4.3)
4—extremely dense	2,920 (5.4)	43 (27)	21 (16)	14.7 (10.7–19.8)	9.2 (6.1–13.4)	7.2 (4.5–11.0)	5.5 (3.1–8.9)

(Continued on the following page)

Table 1. Distribution of variables, number of cancers, and cancer rates in women with a PHBC who participated in mammography screening (BCSC 1996–2008) (Cont'd)

Variable (proportion missing data for variable where applicable)	Number of screening mammograms (%)	Number of second cancers (number invasive cancers)	Number of interval cancers (number invasive)	Cancer rate per 1,000 screens (95% CI)	Invasive cancer rate per 1,000 screens (95% CI)	Interval cancer rate per 1,000 screens (95% CI)	Invasive interval cancer rate per 1,000 screens (95% CI)
BMI (32.2%)[a]							
Underweight (<18.5)	812 (1.8)	6 (3)	3 (2)	7.4 (2.7–16.0)	3.7 (0.8–10.8)	3.7 (0.8–10.8)	2.5 (0.3–8.9)
Normal (18.5–24.9)	19,803 (43.0)	197 (149)	81 (73)	9.9 (8.6–11.4)	7.5 (6.4–8.8)	4.1 (3.2–5.1)	3.7 (2.9–4.6)
Overweight (25–29.9)	15,033 (32.7)	154 (113)	44 (36)	10.2 (8.7–12.0)	7.5 (6.2–9.0)	2.9 (2.1–3.9)	2.4 (1.7–3.3)
Obese I (30–34.9)	6,767 (14.7)	85 (64)	26 (24)	12.6 (10.0–15.5)	9.5 (7.3–12.1)	3.8 (2.5–5.6)	3.5 (2.3–5.3)
Obese II–III (35+)	3,594 (7.8)	43 (33)	12 (8)	12.0 (8.7–16.1)	9.2 (6.3–12.9)	3.3 (1.7–5.8)	2.2 (1.0–4.4)
Time since last mammogram[b] (1.8%)							
9–14 mo	55,354 (83.1)	546 (399)	195 (164)	9.9 (9.1–10.7)	7.2 (6.5–7.9)	3.5 (3.0–4.1)	3.0 (2.5–3.5)
15–23 mo	8,350 (12.5)	88 (71)	25 (23)	10.5 (8.5–13.0)	8.5 (6.6–10.7)	3.0 (1.9–4.4)	2.8 (1.7–4.1)
24+ mo	2,900 (4.4)	46 (37)	15 (14)	15.9 (11.6–21.1)	12.8 (9.0–17.5)	5.2 (2.9–8.5)	4.8 (2.6–8.1)
Type of mammogram (0.03%)							
Film screen	61,514 (90.7)	624 (468)	214 (184)	10.1 (9.4–11.0)	7.6 (6.9–8.3)	3.5 (3.0–4.0)	3.0 (2.6–3.5)
Digital	6,288 (9.3)	73 (52)	26 (22)	11.6 (9.1–14.6)	8.3 (6.2–10.8)	4.1 (2.7–6.1)	3.5 (2.2–5.3)
Time since first breast cancer diagnosis							
<1 y (6–11 mo)	4,762 (7.0)	54 (33)	19 (14)	11.3 (8.5–14.8)	6.9 (4.8–9.7)	4.0 (2.4–6.2)	2.9 (1.6–4.9)
1–2 y	15,486 (22.8)	139 (108)	54 (51)	9.0 (7.6–10.6)	7.0 (5.7–8.4)	3.5 (2.6–4.5)	3.3 (2.5–4.3)
3–4 y	15,988 (23.6)	147 (108)	60 (52)	9.2 (7.8–10.8)	6.8 (5.5–8.1)	3.8 (2.9–4.8)	3.3 (2.4–4.3)
5–6 y	12,469 (18.4)	134 (106)	37 (34)	10.7 (9.0–12.7)	8.5 (7.0–10.3)	3.0 (2.1–4.1)	2.7 (1.9–3.8)
7–9 y	11,562 (17.0)	127 (94)	42 (34)	11.0 (9.2–13.1)	8.1 (6.6–9.9)	3.6 (2.6–4.9)	2.9 (2.0–4.1)
≥10 y	7,552 (11.1)	96 (71)	28 (21)	12.7 (10.3–15.5)	9.4 (7.3–11.8)	3.7 (2.5–5.4)	2.8 (1.7–4.2)
Mode of detection of first cancer (38.7%)							
Screen-detected	26,429 (63.5)	235 (162)	63 (54)	8.9 (7.8–10.1)	6.1 (5.2–7.1)	2.4 (1.8–3.0)	2.0 (1.5–2.7)
Interval cancer in screening	4,346 (10.4)	52 (41)	20 (16)	12.0 (8.9–15.7)	9.4 (6.8–12.8)	4.6 (2.8–7.1)	3.7 (2.1–6.0)
Clinical/diagnostic detected	8,238 (19.8)	98 (80)	51 (44)	11.9 (9.7–14.5)	9.7 (7.7–12.1)	6.2 (4.6–8.1)	5.3 (3.9–7.2)
Other	2,578 (6.2)	30 (22)	8 (7)	11.6 (7.9–16.6)	8.5 (5.4–12.9)	3.1 (1.3–6.1)	2.7 (1.1–5.6)
Age at first breast cancer, y							
<40	2,701 (4.0)	47 (41)	29 (26)	17.4 (12.8–23.1)	15.2 (10.9–20.5)	10.7 (7.2–15.4)	9.6 (6.3–14.1)
40–49	13,688 (20.2)	170 (120)	63 (52)	12.4 (10.6–14.4)	8.8 (7.3–10.5)	4.6 (3.5–5.9)	3.8 (2.8–5.0)
50—59	18,192 (26.8)	166 (109)	48 (41)	9.1 (7.8–10.6)	6.0 (4.9–7.2)	2.6 (1.9–3.5)	2.3 (1.6–3.1)
60–69	17,411 (25.7)	169 (131)	56 (48)	9.7 (8.3–11.3)	7.5 (6.3–8.9)	3.2 (2.4–4.2)	2.8 (2.0–3.7)
70–79	12,649 (18.7)	121 (101)	37 (32)	9.6 (7.9–11.4)	8.0 (6.5–9.7)	2.9 (2.1–4.0)	2.5 (1.7–3.6)
80+	3,178 (4.7)	24 (18)	7 (7)	7.6 (4.8–11.2)	5.7 (3.4–8.9)	2.2 (0.9–4.5)	2.2 (0.9–4.5)

(Continued on the following page)

Published OnlineFirst March 19, 2013; DOI: 10.1158/1055-9965.EPI-12-1208-T

Table 1. Distribution of variables, number of cancers, and cancer rates in women with a PHBC who participated in mammography screening (BCSC 1996–2008) (Cont'd)

Variable (proportion missing data for variable where applicable)	Number of screening mammograms (%)	Number of second cancers (number invasive cancers)	Number of interval cancers (number invasive)	Cancer rate per 1,000 screens (95% CI)	Invasive cancer rate per 1,000 screens (95% CI)	Interval cancer rate per 1,000 screens (95% CI)	Invasive interval cancer rate per 1,000 screens (95% CI)
Type of first breast cancer							
DCIS	13,958 (20.6)	212 (133)	57 (45)	15.2 (13.2–17.4)	9.5 (8.0–11.3)	4.1 (3.1–5.3)	3.2 (2.4–4.3)
Invasive cancer	53,861 (79.4)	485 (387)	183 (161)	9.0 (8.2–9.8)	7.2 (6.5–7.9)	3.4 (2.9–3.9)	3.0 (2.5–3.5)
Stage of first breast cancer							
0	13,958 (20.6)	212 (133)	57 (45)	15.2 (13.2–17.4)	9.5 (8.0–11.3)	4.1 (3.1–5.3)	3.2 (2.4–4.3)
I	32,607 (48.1)	302 (239)	106 (94)	9.3 (8.3–10.4)	7.3 (6.4–8.3)	3.3 (2.7–3.9)	2.9 (2.3–3.5)
II–IIA	15,405 (22.7)	124 (106)	47 (41)	8.0 (6.7–9.6)	6.9 (5.6–8.3)	3.1 (2.2–4.1)	2.7 (1.9–3.6)
IIB	5,849 (8.6)	59 (42)	30 (26)	10.1 (7.7–13.0)	7.2 (5.2–9.7)	5.1 (3.5–7.3)	4.4 (2.9–6.5)
Node status of first invasive cancer[c]							
No metastases	41,764 (77.5)	371 (296)	132 (116)	8.9 (8.0–9.8)	7.1 (6.3–7.9)	3.2 (2.6–3.7)	2.8 (2.3–3.3)
Metastases	12,097 (22.5)	114 (91)	51 (45)	9.4 (7.8–11.3)	7.5 (6.1–9.2)	4.2 (3.1–5.5)	3.7 (2.7–5.0)
Grade of first DCIS cancer[d] (55.9%)							
Grade I	1,134 (18.4)	18 (14)	4 (4)	15.9 (9.4–25.0)	12.3 (6.8–20.6)	3.5 (1.0–9.0)	3.5 (1.0–9.0)
Grade II	2,163 (35.2)	30 (15)	7 (7)	13.9 (9.4–19.7)	6.9 (3.9–11.4)	3.2 (1.3–6.7)	3.2 (1.3–6.7)
Grade III	2,853 (46.4)	48 (32)	15 (12)	16.8 (12.4–22.2)	11.2 (7.7–15.8)	5.3 (2.9–8.7)	4.2 (2.2–7.3)
Grade of first invasive cancer[c] (18.2%)							
Grade I	10,287 (23.4)	85 (69)	22 (20)	8.3 (6.6–10.2)	6.7 (5.2–8.5)	2.1 (1.3–3.2)	1.9 (1.2–3.0)
Grade II	18,863 (42.8)	156 (122)	57 (52)	8.3 (7.0–9.7)	6.5 (5.4–7.7)	3.0 (2.3–3.9)	2.8 (2.1–3.6)
Grade III	14,891 (33.8)	146 (113)	73 (62)	9.8 (8.3–11.5)	7.6 (6.3–9.1)	4.9 (3.8–6.2)	4.2 (3.2–5.3)
Hormone receptor status of DCIS first cancer[d] (88.0%)							
ER+ or PR+	1,328 (79.0)	23 (17)	6 (6)	17.3 (11.0–25.9)	12.8 (7.5–20.4)	4.5 (1.7–9.8)	4.5 (1.7–9.8)
ER− and PR−	352 (21.0)	3 (3)	2 (2)	8.5 (1.8–24.7)	8.5 (1.8–24.7)	5.7 (0.7–20.4)	5.7 (0.7–20.4)
Hormone receptor status of invasive first cancer[c] (21.0%)							
ER+ or PR+	35,870 (84.3)	281 (224)	99 (89)	7.8 (6.9–8.8)	6.2 (5.5–7.1)	2.8 (2.2–3.4)	2.5 (2.0–3.1)
ER− and PR−	6,689 (15.7)	68 (55)	30 (26)	10.2 (7.9–12.9)	8.2 (6.2–10.7)	4.5 (3.0–6.4)	3.9 (2.5–5.7)
Primary surgery (3.3%)							
Mastectomy	24,146 (36.8)	145 (106)	51 (44)	6.0 (5.1–7.1)	4.4 (3.6–5.3)	2.1 (1.6–2.8)	1.8 (1.3–2.4)
Breast conserving with radiation	32,501 (49.6)	365 (278)	130 (112)	11.2 (10.1–12.4)	8.6 (7.6–9.6)	4.0 (3.3–4.7)	3.4 (2.8–4.1)
Breast conserving without radiation	8,912 (13.6)	146 (107)	51 (43)	16.4 (13.8–19.2)	12 (9.8–14.5)	5.7 (4.3–7.5)	4.8 (3.5–6.5)

(Continued on the following page)

Table 1. Distribution of variables, number of cancers, and cancer rates in women with a PHBC who participated in mammography screening (BCSC 1996–2008) (Cont'd)

Variable (proportion missing data for variable where applicable)	Number of screening mammograms (%)	Number of second cancers (number invasive cancers)	Number of interval cancers (number invasive)	Cancer rate per 1,000 screens (95% CI)	Invasive cancer rate per 1,000 screens (95% CI)	Interval cancer rate per 1,000 screens (95% CI)	Invasive interval cancer rate per 1,000 screens (95% CI)
Radiation therapy (4.8%)							
None	29,025 (45.0)	265 (191)	91 (77)	9.1 (8.1–10.3)	6.6 (5.7–7.6)	3.1 (2.5–3.8)	2.7 (2.1–3.3)
Any	35,524 (55.0)	385 (293)	138 (119)	10.8 (9.8–12.0)	8.2 (7.3–9.2)	3.9 (3.3–4.6)	3.3 (2.8–4.0)
Adjuvant systemic therapy (6.5%)							
None	31,990 (50.5)	387 (273)	109 (91)	12.1 (10.9–13.4)	8.5 (7.6–9.6)	3.4 (2.8–4.1)	2.8 (2.3–3.5)
Endocrine therapy only[e]	16,085 (25.4)	113 (89)	45 (40)	7.0 (5.8–8.4)	5.5 (4.4–6.8)	2.8 (2.0–3.7)	2.5 (1.8–3.4)
Chemotherapy only	8,956 (14.1)	94 (79)	49 (43)	10.5 (8.5–12.8)	8.8 (7.0–11.0)	5.5 (4.1–7.2)	4.8 (3.5–6.5)
Chemotherapy and endocrine therapy	6,360 (10.0)	47 (39)	20 (19)	7.4 (5.4–9.8)	6.1 (4.4–8.4)	3.1 (1.9–4.9)	3.0 (1.8–4.7)
Self-reported history of breast implant, reduction, or reconstruction (27.0%)[a]							
No	46,367 (93.6)	468 (353)	154 (130)	10.1 (9.2–11.0)	7.6 (6.8–8.4)	3.3 (2.8–3.9)	2.8 (2.3–3.3)
Yes	3,172 (6.4)	15 (10)	7 (6)	4.7 (2.6–7.8)	3.2 (1.5–5.8)	2.2 (0.9–4.5)	1.9 (0.7–4.1)

NOTE: Number of cancers refers to any second breast cancer (ipsilateral in-breast recurrence or new cancer, or contralateral breast cancer) in women with a PHBC.

[a]One site was removed from each of these variables due to high proportion of missing values at that site.

[b]Refers to any (screening or diagnostic) mammogram only in calculation of time since last mammogram.

[c]Based on women with a prior history of invasive breast cancer.

[d]Based on women with a prior history of DCIS.

[e]Includes 19 women with a prior history of DCIS who reportedly had chemotherapy (12 with chemotherapy only; 7 with both endocrine and chemotherapy).

Published OnlineFirst March 19, 2013; DOI: 10.1158/1055-9965.EPI-12-1208-T

Table 2. Univariate models of the probability of screen-detected or interval invasive, or DCIS, second breast cancer (no second cancer as referent) within 1 year of screening (based on 13,958 screening mammograms) in PHBC women with history of *DCIS* (BCSC 1996–2008)

Variable (proportion missing data for variable where applicable)	Screen-detected invasive second breast cancer OR (95% CI)	Interval invasive breast cancer OR (95% CI)	DCIS second breast cancer OR (95% CI)	*P*[a]
Age at mammography, y				
<50	1.98 (0.79–4.96)	**4.68 (1.71–12.77)**	2.10 (0.99–4.45)	**0.0101**
50—59	1.79 (0.86–3.75)	1.44 (0.51–4.04)	1.38 (0.71–2.67)	
60—69	Referent	Referent	Referent	
70—79	**2.52 (1.24–5.14)**	**2.66 (1.02–6.94)**	1.00 (0.47–2.10)	
80+	**2.56 (1.12–5.84)**	0.78 (0.16–3.90)	1.32 (0.55–3.13)	
Race/ethnicity (3.5%)				
White, non-Hispanic	Referent	Referent	Referent	0.74
Black, non-Hispanic	1.25 (0.28–5.51)	1.54 (0.33–7.23)	0.60 (0.08–4.64)	
Hispanic	1.03 (0.43–2.42)	0.75 (0.16–3.48)	0.96 (0.27–3.42)	
Asian, Pacific Islander	0.52 (0.07–3.82)	2.55 (0.57–11.37)	2.70 (0.92–7.87)	
First-degree family history of breast cancer (17.6%)				
No	Referent	Referent	Referent	**0.021**
Yes	**2.15 (1.27–3.64)**	1.29 (0.62–2.70)	1.37 (0.78–2.38)	
Menopausal status (9.5%)				
Post	Referent	Referent	Referent	**0.0004**
Pre, Peri	1.56 (0.76–3.21)	**2.36 (1.06–5.28)**	**2.89 (1.61–5.18)**	
BI-RADS breast density (19.6%)				
1—almost entirely fatty	0.73 (0.17–3.17)	1.35 (0.39–4.76)	0.33 (0.04–2.49)	0.60
2—scattered fibroglandular tissue	referent	Referent	Referent	
3–heterogeneously dense	1.42 (0.77–2.59)	1.09 (0.52–2.29)	1.60 (0.90–2.82)	
4—extremely dense	1.31 (0.44–3.91)	0.90 (0.20–4.00)	1.99 (0.79–5.01)	
BMI (36.6%)[b]				
Normal (18.5–24.9)	Referent	Referent	Referent	0.66
Overweight(25–29.9)	1.58 (0.87–2.88)	0.89 (0.37–2.14)	1.35 (0.68–2.69)	
Obese I (30–34.9)	1.87 (0.87–4.00)	1.43 (0.51–4.05)	1.64 (0.70–3.82)	
Obese II–III (35+)	2.20 (0.88–5.52)	1.11 (0.25–4.98)	1.14 (0.33–3.93)	
Time since last mammogram (1.7%)				
9–14 mo	Referent	Referent	Referent	0.58
15–23 mo	0.96 (0.49–1.89)	0.75 (0.26–2.13)	0.95 (0.45–2.01)	
24+ mo	0.80 (0.25–2.57)	2.23 (0.77–6.45)	1.90 (0.75–4.82)	
Type of mammogram (0.02%)				
Film screen	Referent	Referent	Referent	0.73
Digital	0.79 (0.31–2.05)	0.54 (0.15–1.93)	1.16 (0.55–2.42)	
Time since first breast cancer diagnosis				
<1 y (6–11 mo)	1.22 (0.34–4.47)	0.64 (0.14–2.89)	1.43 (0.51–4.04)	0.66
1–2 y	Referent	Referent	Referent	
3–4 y	1.53 (0.70–3.35)	0.76 (0.33–1.76)	1.35 (0.66–2.74)	
5–6 y	**2.62 (1.24–5.53)**	0.80 (0.32–1.95)	1.32 (0.62–2.82)	
7–9 y	1.66 (0.73–3.76)	0.67 (0.25–1.81)	1.05 (0.46–2.42)	
≥10 y	1.04 (0.41–2.61)	0.51 (0.16–1.66)	1.28 (0.54–3.02)	
Mode of detection of first cancer (41.1%)				
Screen-detected	Referent	Referent	Referent	0.67
Interval cancer in screening	1.64 (0.68–3.94)	1.16 (0.27–5.07)	0.89 (0.27–2.91)	
Clinical/diagnostic detected	1.38 (0.48–3.92)	2.46 (0.81–7.45)	1.61 (0.62–4.17)	
Other	0.81 (0.25–2.68)	2.26 (0.75–6.85)	1.26 (0.44–3.62)	

(Continued on the following page)

Published OnlineFirst March 19, 2013; DOI: 10.1158/1055-9965.EPI-12-1208-T

Table 2. Univariate models of the probability of screen-detected or interval invasive, or DCIS, second breast cancer (no second cancer as referent) within 1 year of screening (based on 13,958 screening mammograms) in PHBC women with history of *DCIS* (BCSC 1996–2008) (Cont'd)

Variable (proportion missing data for variable where applicable)	Screen-detected invasive second breast cancer OR (95% CI)	Interval invasive breast cancer OR (95% CI)	DCIS second breast cancer OR (95% CI)	*P*[a]
Age at first breast cancer, y				
<40	1.16 (0.26–5.14)	2.35 (0.65–8.49)	2.28 (0.64–8.11)	0.17
40—49	1.68 (0.86–3.30)	1.14 (0.52–2.52)	1.75 (0.88–3.48)	
50—59	0.93 (0.44–1.96)	0.60 (0.24–1.47)	1.48 (0.74–2.94)	
60—69	Referent	Referent	Referent	
70—79	**2.36 (1.19–4.66)**	0.64 (0.22–1.82)	1.21 (0.53–2.78)	
80+	1.51 (0.43–5.32)	0.55 (0.07–4.25)	0.54 (0.07–4.18)	
Primary surgery (7.7%)				
Mastectomy	Referent	Referent	Referent	**<.0001**
Breast conserving with radiation	**2.37 (1.15–4.88)**	**4.44 (1.49–13.25)**	**2.74 (1.38–5.45)**	
Breast conserving without radiation	**3.98 (1.92–8.25)**	**6.30 (2.09–19.01)**	**2.68 (1.29–5.57)**	
Radiation therapy (12.5%)				
None	Referent	Referent	Referent	0.15
Any	**0.59 (0.36–0.98)**	0.70 (0.36–1.36)	1.09 (0.64–1.85)	
Adjuvant systemic therapy (13.7%)				
None	Referent	Referent	Referent	**0.035**
Endocrine therapy[c]	0.33 (0.10–1.04)	1.74 (0.79–3.87)	0.40 (0.14–1.10)	
Self-reported history of breast implant, reduction, or reconstruction (27.0%)[b]				
No	Ref	Ref	Ref	0.89
Yes	0.58 (0.13–2.53)	1.17 (0.15–9.09)	0.82 (0.18–3.67)	

NOTE: Each univariate model included the variable of interest and was adjusted for mammography registry and primary surgery received for first breast cancer. OR and *P* values shown in bold indicate statistically significant association.

[a]*P* is the global *P* value for each univariate analysis in which joint modeling was conducted for the 3 outcomes (screen-detected or interval invasive, or DCIS, second breast cancer) with no cancer as the referent category.

[b]One site was removed due to high proportion of missing values for variable at that site (for BMI, 141 women who were reportedly "underweight" were excluded).

[c]Includes 19 women with a prior history of DCIS who reportedly had chemotherapy (12 with chemotherapy only; 7 with both endocrine and chemotherapy).

"breasts at risk" (hence unilateral mastectomy would approximately halve the risk of another breast cancer) and also evidenced in the higher underlying breast cancer rates in PHBC women who had initial breast conservation (Table 1), we found that screens of women who had breast conservation without radiation had more than 4 times increased risk of screen-detected or interval invasive second breast cancer. The finding that women ages 70 to 79 years with a history of DCIS had increased risk for both screen-detected invasive breast cancer and interval invasive breast cancer (relative to the younger referent age group, Table 4) indicates a higher underlying risk in this age group and suggests an age-related biologic basis for increased risk of developing invasive breast cancer in women with DCIS first cancer.

The model in women with invasive first breast cancer (Table 5) highlighted that risk in this group was relatively complex and driven by several factors, including first breast cancer surgical treatment (in this group, ORs for breast conservation showed the expected approximate "doubling" of risk relative to mastectomy). Importantly, in women with invasive first cancer, variables that predominantly and significantly increased the odds of an interval invasive breast cancer were younger age at first breast cancer diagnosis, "extremely dense" breasts, first-degree breast cancer family history, and breast conservation (with/without radiation). In women with an invasive first breast cancer (Table 5), adjuvant endocrine therapy predicted reduced risk of screen-detected second breast cancer and of DCIS; chemotherapy alone was not significantly associated with risk. Systemic therapy of any type did not affect the risk of an interval breast cancer. Fatty (relative to dense) breasts predicted reduced risk of DCIS and of an interval invasive breast cancer in women with an invasive first breast cancer. Although we cannot explain the finding that first breast cancer stage (IIB) had higher odds of DCIS as the second breast cancer, we noted that a relatively high proportion of women with stage IIB first

Published OnlineFirst March 19, 2013; DOI: 10.1158/1055-9965.EPI-12-1208-T

Table 3. Univariate models of the probability of screen-detected or interval invasive, or DCIS, second breast cancer (no second cancer as referent) within 1 year of screening (based on 53,861 screening mammograms) in PHBC women with history of invasive breast cancer (BCSC 1996–2008)

Variable (proportion missing data where applicable)	Screen-detected invasive second breast cancer OR (95% CI)	Interval invasive breast cancer OR (95% CI)	DCIS second breast cancer OR (95% CI)	*P*[a]
Age at mammography, y				
<50	0.98 (0.62–1.55)	**2.88 (1.73–4.80)**	0.90 (0.46–1.78)	**0.0069**
50–59	0.71 (0.48–1.05)	1.56 (0.96–2.56)	0.82 (0.47–1.40)	
60–69	Referent	Referent	Referent	
70–79	0.86 (0.59–1.24)	1.56 (0.95–2.56)	0.58 (0.32–1.06)	
80+	0.93 (0.60–1.43)	0.99 (0.51–1.94)	0.72 (0.36–1.43)	
Race/ethnicity (3.9%)				
White, non-Hispanic	Referent	Referent	Referent	0.50
Black, non-Hispanic	1.07 (0.45–2.55)	2.18 (0.92–5.14)	1.28 (0.29–5.67)	
Hispanic	0.51 (0.23–1.13)	1.51 (0.82–2.80)	1.34 (0.52–3.46)	
Asian, Pacific Islander	0.97 (0.35–2.63)	0.97 (0.24–4.00)	0.57 (0.08–4.16)	
First-degree family history of breast cancer (15.5%)				
No	Referent	Referent	Referent	**0.038**
Yes	1.33 (0.96–1.84)	**1.46 (1.01–2.11)**	1.34 (0.84–2.15)	
Menopausal status (13.1%)				
Post	Referent	Referent	Referent	**<.0001**
Pre, peri	1.13 (0.68–1.90)	**2.65 (1.67–4.19)**	**2.04 (1.10–3.79)**	
BI-RADS breast density (20.5%)				
1—almost entirely fatty	0.60 (0.30–1.20)	0.26 (0.06–1.07)	0.64 (0.19–2.12)	**0.0008**
2—scattered fibroglandular tissue	Referent	Referent	Referent	
3—heterogeneously dense	0.96 (0.70–1.32)	**1.63 (1.09–2.42)**	1.51 (0.91–2.51)	
4—extremely dense	0.73 (0.34–1.58)	**2.78 (1.49–5.18)**	**2.74 (1.24–6.06)**	
BMI (31.0%)[b]				
Normal (18.5–24.9)	Referent	Referent	Referent	0.29
Overweight(25–29.9)	1.27 (0.86–1.88)	0.61 (0.39–0.96)	0.89 (0.50–1.56)	
Obese I (30–34.9)	1.40 (0.87–2.26)	0.86 (0.51–1.47)	0.98 (0.49–1.96)	
Obese II–III (35+)	1.71 (0.99–2.95)	0.52 (0.22–1.20)	1.05 (0.46–2.41)	
Time since last mammogram (1.8%)				
9–14 mo	Referent	Referent	Referent	**0.018**
15–23 mo	1.44 (0.98–2.11)	1.05 (0.64–1.7)	0.82 (0.41–1.65)	
24+ mo	**2.43 (1.46–4.05)**	1.35 (0.66–2.79)	0.59 (0.14–2.41)	
Type of mammogram (0.03%)				
Film screen	Referent	Referent	Referent	0.53
Digital	1.05 (0.65–1.69)	1.04 (0.61–1.80)	0.56 (0.26–1.22)	
Time since first breast cancer diagnosis				
<1 y (6–11 mo)	0.78 (0.39–1.56)	1.00 (0.52–1.92)	**2.19 (1.01–4.72)**	**0.036**
1–2 y	Referent	Referent	Referent	
3–4 y	0.78 (0.50–1.23)	0.95 (0.60–1.49)	1.02 (0.51–2.02)	
5–6 y	1.26 (0.82–1.92)	0.81 (0.49–1.34)	0.98 (0.47–2.05)	
7–9 y	1.36 (0.89–2.08)	0.99 (0.61–1.62)	1.77 (0.92–3.38)	
≥10 y	**1.79 (1.14–2.82)**	0.99 (0.54–1.81)	1.98 (0.96–4.08)	
Mode of detection of first cancer (38.0%)				
Screen-detected	Referent	Referent	Referent	**0.0011**
Interval cancer in screening	1.35 (0.78–2.34)	**2.12 (1.14–3.95)**	1.00 (0.44–2.26)	
Clinical/diagnostic detected	1.24 (0.80–1.93)	**3.07 (1.91–4.93)**	0.75 (0.38–1.49)	
Other	1.74 (0.91–3.32)	0.94 (0.29–3.06)	1.19 (0.42–3.36)	

(Continued on the following page)

Published OnlineFirst March 19, 2013; DOI: 10.1158/1055-9965.EPI-12-1208-T

Table 3. Univariate models of the probability of screen-detected or interval invasive, or DCIS, second breast cancer (no second cancer as referent) within 1 year of screening (based on 53,861 screening mammograms) in PHBC women with history of invasive breast cancer (BCSC 1996–2008) (Cont'd)

Variable (proportion missing data where applicable)	Screen-detected invasive second breast cancer OR (95% CI)	Interval invasive breast cancer OR (95% CI)	DCIS second breast cancer OR (95% CI)	P^a
Age at first breast cancer, y				
<40	1.32 (0.72–2.41)	**3.67 (2.13–6.34)**	0.76 (0.23–2.53)	**0.0001**
40–49	0.91 (0.62–1.36)	1.30 (0.81–2.09)	1.22 (0.68–2.18)	
50–59	0.76 (0.52–1.11)	0.87 (0.54–1.41)	1.16 (0.67–1.99)	
60–69	Referent	Referent	Referent	
70–79	0.86 (0.58–1.28)	1.06 (0.64–1.76)	0.54 (0.26–1.13)	
80+	0.60 (0.29–1.26)	0.73 (0.28–1.88)	0.72 (0.25–2.09)	
Stage of first breast cancer				
I	Referent	Referent	Referent	**0.0049**
II–IIA	1.11 (0.82–1.50)	1.08 (0.74–1.57)	0.69 (0.40–1.19)	
IIB	0.75 (0.44–1.30)	**1.95 (1.24–3.06)**	**1.84 (1.05–3.22)**	
Node status of first cancer				
No metastases	Referent	Referent	Referent	0.91
Metastases	1.02 (0.64–1.64)	1.24 (0.70–2.17)	0.96 (0.43–2.13)	
Grade of first cancer—invasive (18.2%)				
Grade I	Referent	Referent	Referent	0.12
Grade II	0.85 (0.58–1.24)	1.37 (0.81–2.32)	1.13 (0.62–2.06)	
Grade III	0.84 (0.56–1.27)	2.00 (1.19–3.38)	1.40 (0.75–2.62)	
Hormone receptor status of first cancer (21.0%)				
ER+ or PR+	Referent	Referent	Referent	0.09
ER− and PR−	1.24 (0.82–1.87)	**1.66 (1.06–2.59)**	1.24 (0.66–2.33)	
Primary surgery (2.2%)				
Mastectomy	Referent	Referent	Referent	**<.0001**
Breast conserving with radiation	**1.78 (1.28–2.48)**	1.87 (1.27–2.75)	1.38 (0.85–2.23)	
Breast conserving without radiation	**2.28 (1.43–3.65)**	**2.41 (1.42–4.07)**	**2.16 (1.11–4.20)**	
Radiation therapy (2.8%)				
None	Referent	Referent	Referent	0.19
Any	0.85 (0.58–1.24)	0.82 (0.54–1.25)	0.61 (0.36–1.05)	
Adjuvant systemic therapy (4.7%)				
None	Referent	Referent	Referent	**0.0005**
Endocrine therapy only	**0.56 (0.39–0.80)**	0.83 (0.54–1.29)	0.54 (0.31–0.93)	
Chemotherapy only	0.79 (0.53–1.20)	**1.77 (1.14–2.74)**	0.59 (0.30–1.13)	
Chemotherapy and endocrine therapy	**0.56 (0.33–0.96)**	1.18 (0.67–2.08)	0.46 (0.20–1.03)	
Self-reported history of breast implant, reduction, or reconstruction (26.9%)[b]				
No	Referent	Referent	Referent	0.22
Yes	**0.23 (0.06–0.95)**	1.04 (0.42–2.62)	0.72 (0.22–2.35)	

NOTE: Each univariate model included the variable of interest and was adjusted for mammography registry, primary surgery received for first breast cancer, and stage of first invasive cancer. OR and *P* values shown in bold indicate statistically significant association.
Abbreviations: ER. Estrogen receptor; PR, progesterone receptor.
[a]*P* is the global *P* value for each univariate analysis in which joint modeling was conducted for the three outcomes (screen-detected or interval invasive, or DCIS, second breast cancer) with no cancer as the referent category.
[b]One site was removed due to high proportion of missing values for variable at that site.

cancer, and DCIS on follow-up, had received breast conservation without radiation. It is possible that residual confounding explains this finding despite adjusting for associated variables in the model. This may also be due to more intensive surveillance in stage IIB women.

Our models provide information on risk factors to support informed discussion of tailored adjunct screening or more frequent mammographic screening (28) in PHBC; however, this work does not assess the impact of tailored breast screening in these women. Our findings

Published OnlineFirst March 19, 2013; DOI: 10.1158/1055-9965.EPI-12-1208-T

Table 4: Multivariable model of the probability of screen-detected or interval invasive, or DCIS, second breast cancer (no second cancer as referent) within 1 year of screening (based on 11,205 screening mammograms) in PHBC women with history of *DCIS* (BCSC 1996–2008)

Variable	Screen-detected invasive second breast cancer OR (95% CI)	Interval invasive breast cancer OR (95% CI)	DCIS second breast cancer OR (95% CI)	*P*[a]
Age at mammography, y				
<50	0.96 (0.20–4.58)	2.75 (0.43–17.57)	0.81 (0.24–2.74)	0.40
50–59	1.18 (0.54–2.61)	1.36 (0.42–4.37)	1.00 (0.48–2.11)	
60–69	Referent	Referent	Referent	
70–79	**2.14 (1.09–4.19)**	**3.06 (1.08–8.62)**	0.91 (0.42–1.95)	
80+	1.99 (0.88–4.50)	1.52 (0.36–6.47)	1.00 (0.38–2.61)	
First-degree family history of breast cancer				
No	Referent	Referent	Referent	0.13
Yes	1.66 (0.99–2.79)	1.29 (0.61–2.71)	1.43 (0.81–2.54)	
Menopausal status				
Post	Referent	Referent	Referent	0.21
Pre, peri	1.72 (0.43–6.87)	1.42 (0.28–7.19)	2.73 (0.97–7.70)	
BI-RADS breast density				
1—almost entirely fatty	0.62 (0.14–2.65)	0.90 (0.20–4.07)	0.36 (0.06–2.16)	0.63
2—scattered fibroglandular tissue	Referent	Referent	Referent	
3—heterogeneously dense	1.40 (0.77–2.53)	1.28 (0.59–2.80)	1.41 (0.77–2.58)	
4—extremely dense	1.39 (0.48–4.05)	1.07 (0.22–5.25)	2.11 (0.81–5.44)	
BMI				
Normal (18.5–24.9)	Referent	Referent	Referent	0.14
Overweight(25–29.9)	1.57 (0.90–2.75)	0.99 (0.41–2.39)	1.81 (0.91–3.61)	
Obese I (30–34.9)	2.32 (1.17–4.59)	1.47 (0.48–4.47)	2.24 (0.95–5.23)	
Obese II–III (35+)	2.96 (1.19–7.34)	1.13 (0.27–4.65)	1.82 (0.52–6.29)	
Primary surgery				
Mastectomy	Referent	Referent	Referent	**0.0001**
Breast conserving with radiation	**3.24 (1.39–7.55)**	**3.23 (1.07–9.73)**	**2.57 (1.26–5.24)**	
Breast conserving without radiation	**4.82 (2.04–11.35)**	**4.05 (1.31–12.51)**	**2.90 (1.37–6.15)**	
Adjuvant systemic therapy				
None	Referent	Referent	Referent	0.091
Endocrine therapy[b]	0.36 (0.11–1.16)	1.60 (0.65–3.95)	0.40 (0.12–1.28)	

NOTE: Model also adjusted for mammography registry (screens from one site were removed from model due to high proportion of missing values for BMI). OR and *P* values shown in bold indicate statistically significant association.

[a]*P* value for each variable in multivariate analysis using joint modeling for the three outcomes (screen-detected or interval invasive, or DCIS, second breast cancer) with no cancer as the referent category.

[b]Includes 19 women with a history of DCIS who reportedly had chemotherapy (12 with chemotherapy only; 7 with both endocrine and chemotherapy).

should therefore not be taken to imply benefit from adjunct or more frequent screening in PHBC, and should consider that to date, there are no data indicating improved clinical endpoints in PHBC through adjunct breast screening. In addition, the potential value of adjunct screening will not only depend on interval breast cancer risk but also on the woman's absolute risk of developing a second breast cancer, her life-expectancy, and first breast cancer–related prognosis. Our results for *interval* invasive breast cancer can however guide adjunct screening research by targeting PHBC women at increased risk of interval breast cancer, for example, those who received breast conservation without radiation. Other specific groups at ≥2 times increased risk of an interval invasive breast cancer were 70 to 79 year old women with history of DCIS, and women with invasive first breast cancer who had extremely dense breasts or who were less than 40 years at first breast cancer diagnosis—although OR estimates varied depending on the referent category, there was consistent evidence of increased risk of an interval breast cancer in women < 40 years at first breast cancer diagnosis. It is likely that this partly reflects women with hereditary risk and/or breast cancer susceptibility genes (although we did not

Published OnlineFirst March 19, 2013; DOI: 10.1158/1055-9965.EPI-12-1208-T

Table 5. Multivariable model of the probability of screen-detected or interval invasive, or DCIS, second breast cancer (no second cancer as referent) within 1 year of screening (based on 46,303 screening mammograms) in PHBC women with history of *invasive* breast cancer (BCSC 1996–2008)

Variable	Screen-detected invasive second breast cancer OR (95% CI)	Interval invasive breast cancer OR (95% CI)	DCIS second breast cancer OR (95% CI)	*P*[a]
First-degree family history of breast cancer				
No	Referent	Referent	Referent	**0.021**
Yes	1.31 (0.96–1.80)	**1.54 (1.07–2.22)**	1.38 (0.85–2.22)	
Menopausal status				
Post	Referent	Referent	Referent	0.36
Pre, peri	0.99 (0.49–2.01)	0.79 (0.36–1.73)	2.26 (0.83–6.19)	
BI-RADS breast density				
1—almost entirely fatty	0.60 (0.31–1.15)	0.43 (0.11–1.62)	0.60 (0.20–1.77)	**0.016**
2—scattered fibroglandular tissue	Referent	Referent	Referent	
3—heterogeneously dense	0.98 (0.70–1.36)	1.43 (0.94–2.20)	1.45 (0.88–2.38)	
4—extremely dense	0.88 (0.41–1.86)	**2.55 (1.40–4.67)**	2.33 (0.96–5.67)	
BMI				
Normal (18.5–24.9)	Referent	Referent	Referent	0.90
Overweight (25–29.9)	1.18 (0.80–1.75)	0.79 (0.51–1.21)	1.15 (0.66–1.98)	
Obese I (30–34.9)	1.22 (0.78–1.91)	1.05 (0.63–1.74)	1.29 (0.65–2.56)	
Obese II–III (35+)	1.38 (0.79–2.43)	0.80 (0.36–1.77)	1.28 (0.57–2.86)	
Time since last mammogram				
9–14 mo	Referent	Referent	Referent	**0.048**
15+ mo	**1.59 (1.14–2.22)**	1.03 (0.66–1.62)	0.77 (0.40–1.46)	
Time since first breast cancer diagnosis				
< 1 y (6–11 mo)	1.34 (0.71–2.55)	1.01 (0.51–2.00)	1.92 (0.89–4.13)	0.060
1–2 y	Referent	Referent	Referent	
3–4 y	0.84 (0.52–1.37)	0.91 (0.56–1.46)	1.06 (0.54–2.07)	
5–6 y	1.43 (0.92–2.25)	0.78 (0.46–1.33)	0.86 (0.40–1.86)	
7+ y	**1.52 (1.00–2.32)**	0.98 (0.61–1.57)	**1.87 (1.01–3.49)**	
Age at first breast cancer, y				
< 40	1.11 (0.43–2.82)	**3.41 (1.34–8.70)**	0.35 (0.07–1.66)	**0.023**
40–49	0.90 (0.55–1.46)	0.99 (0.54–1.82)	0.83 (0.37–1.90)	
50–59	0.79 (0.54–1.17)	0.74 (0.45–1.23)	1.24 (0.72–2.13)	
60–69	Referent	Referent	Referent	
70–79	0.92 (0.61–1.38)	1.09 (0.65–1.83)	0.44 (0.20–1.00)	
80+	0.53 (0.23–1.25)	0.73 (0.28–1.90)	0.99 (0.37–2.67)	
Stage of first breast cancer				
I	Referent	Referent	Referent	**0.0317**
II–IIA	1.02 (0.72–1.46)	0.92 (0.60–1.41)	0.83 (0.46–1.50)	
IIB	0.84 (0.47–1.49)	1.46 (0.86–2.47)	**2.46 (1.30–4.67)**	
Primary surgery				
Mastectomy	Referent	Referent	Referent	<**0.001**
Breast conserving with radiation	**1.77 (1.24–2.53)**	**1.78 (1.18–2.69)**	1.52 (0.91–2.52)	
Breast conserving without radiation	**1.95 (1.17–3.27)**	**2.67 (1.53–4.65)**	**2.29 (1.15–4.56)**	
Adjuvant systemic therapy				
None	Referent	Referent	Referent	**0.0194**
Endocrine therapy only	**0.60 (0.41–0.87)**	0.78 (0.50–1.23)	**0.55 (0.32–0.94)**	
Chemotherapy only	0.87 (0.55–1.38)	1.23 (0.75–2.02)	0.53 (0.27–1.02)	
Chemotherapy and endocrine therapy	0.71 (0.41–1.21)	1.01 (0.56–1.84)	**0.35 (0.15–0.84)**	

NOTE: Model also adjusted for mammography registry (screens from one site were removed from model due to high proportion of missing values for BMI). OR and *P* values shown in bold indicate statistically significant association.

[a]*P* value for each variable in multivariate analysis using joint modeling for the 3 outcomes (screen-detected or interval invasive, or DCIS, second breast cancer) with no cancer as the referent category.

Published OnlineFirst March 19, 2013; DOI: 10.1158/1055-9965.EPI-12-1208-T

have the data to investigate this) and reinforces the recommendation to consider genetic counseling in women diagnosed with breast cancer at age <40 years (7, 29).

Screens in PHBC women (whether first DCIS or invasive cancer) who received unilateral mastectomy had relatively reduced risk of all modeled outcomes, as they had one breast at risk: this should not be a reason to preferentially recommend mastectomy for breast cancer treatment, rather it highlights that screening mammography performs adequately in PHBC women who had mastectomy of the affected breast. Although our work focused on short-term risk (within 1 year of screening), the finding that local treatment received for first breast cancer had a dominant influence on risk is in keeping with an analytic model that used lifetime risk to recommend MRI screening (12) and reported that adjunct screening recommendations were sensitive to the type of surgical treatment received for first cancer. To our knowledge, there are no other studies defining risk factors for screen-detected *or* interval breast cancer *or* DCIS in PHBC women, so we cannot compare the results of our models and their accuracy with other research. However, we estimated that our models had moderate accuracy (AUCs = 0.67–0.73) with similar accuracy to breast cancer risk models in the general population (14, 30). Because the accuracy of our models was examined using the same dataset from which the models were developed, accuracy may be overestimated—future research validating the models in PHBC women using an independent dataset would be valuable.

It is likely that some of the women in our study had second breast cancers detected by an adjunct modality, and these cancers might otherwise have been detected by subsequent screening mammography—hence a limitation of our study is the absence of data on women who may have had adjunct screening. Another potential limitation is that first breast cancer mode of detection (reported in Table 1) was excluded in the final models due to many screens missing this information. We did not find an association between mammography type (film vs. digital) in either of our models; however, a relatively small proportion of women had screening with digital mammography in the timeframe of the study.

Our work presents evidence on risk factors for second breast cancers including risk factors for interval invasive breast cancer in PHBC women who had undergone mammography screening. Although the risk of a second breast cancer is modest, and the best way to incorporate the information from our models into clinical decision-making requires evaluation, the evidence provided on risk factors could be used to support discussion of screening in PHBC women. At present, there is a paucity of data on tailored (adjunct and/or more frequent) screening strategies that may potentially reduce interval breast cancers in PHBC women who participate in mammography screening. Therefore, our study provides information that may help clinicians and researchers identify women at increased risk of interval breast cancer to guide formal evaluations to determine whether tailored breast screening reduces the interval breast cancer rate in PHBC women.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: N. Houssami, K. Kerlikowske, D.S.M. Buist, L. Irwig, D.L. Miglioretti
Development of methodology: N. Houssami, K. Kerlikowske, D.S.M. Buist, L. Irwig, D.L. Miglioretti
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): K. Kerlikowske, D.S.M. Buist, D.L. Miglioretti
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): N. Houssami, L.A. Abraham, K. Kerlikowske, D.S.M. Buist, J. Lee, D.L. Miglioretti
Writing, review, and/or revision of the manuscript: N. Houssami, L.A. Abraham, K. Kerlikowske, D.S.M. Buist, L. Irwig, J. Lee, D.L. Miglioretti
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): K. Kerlikowske
Study supervision: N. Houssami, D.S.M. Buist, D.L. Miglioretti

Acknowledgments

The collection of cancer and vital status data used in this study was supported in part by several state public health departments and cancer registries throughout the United States. For a full description of these sources, please see: http://www.breastscreening.cancer.gov/work/acknowledgement.html. The authors thank the participating women, mammography facilities, and radiologists for the data they have provided for this study. A list of the BCSC investigators and procedures for requesting BCSC data for research are provided at: http://breastscreening.cancer.gov/. The Breast Cancer Surveillance Consortium Steering Committee reviewed and approved this manuscript.

Grant Support

N. Houssami receives research support through a National Breast Cancer Foundation (NBCF) Practitioner Fellowship. L. Irwig and N. Houssami are partly supported via National Health and Medical Research Council (NHMRC) program grant 633003 to the Screening & Test Evaluation Program. This work was supported by the National Cancer Institute–funded Breast Cancer Surveillance Consortium (U01CA63740, U01CA86076, U01CA86082, U01CA63736, U01CA70013, U01CA69976, U01CA63731, U01CA70040, HHSN261201100031C).

Received October 31, 2012; revised February 15, 2013; accepted March 4, 2013; published OnlineFirst March 19, 2013.

References

1. Lash TL, Fox MP, Buist DS, Wei F, Field TS, Frost FJ, et al. Mammography surveillance and mortality in older breast cancer survivors. J Clin Oncol 2007;25:3001–6.
2. Lu WL, Jansen L, Post WJ, Bonnema J, Van de Velde JC, de Bock GH. Impact on survival of early detection of isolated breast recurrences after the primary treatment for breast cancer: a meta-analysis. Breast Cancer Res Treat 2009;114:403–12.
3. Ciatto S, Miccinesi G, Zappa M. Prognostic impact of the early detection of metachronous contralateral breast cancer. Eur J Cancer 2004;40:1496–501.
4. Houssami N, Ciatto S. Mammographic surveillance in women with a personal history of breast cancer: how accurate? How effective? Breast 2010;19:439–45.
5. Khatcheressian JL, Wolff AC, Smith TJ, Grunfeld E, Muss HB, Vogel VG, et al. American Society of Clinical Oncology 2006 update of the breast cancer follow-up and management guidelines in the adjuvant setting. J Clin Oncol 2006;24:5091–7.
6. Schwartz GF, Veronesi U, Clough KB, Dixon JM, Fentiman IS, Heywang-Kobrunner SH, et al.. Consensus conference on breast conservation. J Am Coll Surg 2006;203:198–207.

Published OnlineFirst March 19, 2013; DOI: 10.1158/1055-9965.EPI-12-1208-T

7. Hayes DF. Clinical practice. Follow-up of patients with early breast cancer. N Engl J Med 2007;356:2505–13.
8. Carlson RW, Allred DC, Anderson BO, Burstein HJ, Carter WB, Edge SB, et al. Breast cancer. Clinical practice guidelines in oncology. J Natl Compr Cancer Netw 2009;7:122–92.
9. Brennan ME, Houssami N. Overview of long term care of breast cancer survivors. Maturitas 2011;69:106–112.
10. Saslow D, Boetes C, Burke W, Harms S, Leach MO, Lehman CD, et al. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. CA: A Cancer J Clin 2007;57: 75–89.
11. Berg WA, Blume JD, Cormack JB, Mendelson EB, Lehrer D, Bohm-Velez M, et al. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. JAMA 2008;299:2151–63.
12. Punglia RS, Hassett MJ. Using lifetime risk estimates to recommend magnetic resonance imaging screening for breast cancer survivors. J Clin Oncol 2010;28:4108–10.
13. Houssami N, Abraham LA, Miglioretti DL, Sickles EA, Kerlikowske K, Buist DS, et al. Accuracy and outcomes of screening mammography in women with a personal history of early-stage breast cancer. JAMA 2011;305:790–9.
14. Barlow WE, White E, Ballard-Barbash R, Vacek PM, Titus-Ernstoff L, Carney PA, et al. Prospective breast cancer risk prediction model for women undergoing screening mammography. J Natl Cancer Inst 2006;98:1204–14.
15. Gail MH, Brinton LA, Byar DP, Corle DK, Green SB, Schairer C, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst 1989;81:1879–86.
16. Tice JA, Cummings SR, Smith-Bindman R, Ichikawa L, Barlow WE, Kerlikowske K. Using clinical factors and mammographic breast density to estimate breast cancer risk: development and validation of a new predictive model. Ann Intern Med 2008;148: 337–47.
17. Antoniou AC, Pharoah PD, McMullan G, Day NE, Stratton MR, Peto J, et al. A comprehensive model for familial breast cancer incorporating BRCA1, BRCA2 and other genes. Br J Cancer 2002;86:76–83.
18. Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. Stat Med 2004;23:1111–30.
19. Buist DS, Abraham LA, Barlow WE, Krishnaraj A, Holdridge R, Sickles E, et al. Diagnosis of second breast cancer events after initial diagnosis of early stage breast cancer. Breast Cancer Res Treat 2010;124: 863–73.
20. Rosenberg RD, Yankaskas BC, Abraham LA, Sickles EA, Lehman CD, Geller BM, et al. Performance benchmarks for screening mammography. Radiology 2006;241:55–66.
21. Hwang ES, Miglioretti DL, Ballard-Barbash R, Weaver DL, Kerlikowske K, National Cancer Institute Breast Cancer Surveillance Consortium. Association between breast density and subsequent breast cancer following treatment for ductal carcinoma in situ. Cancer Epidemiol, Biomarkers Prev 2007;16:2587–93.
22. Park CC, Rembert J, Chew K, Moore D, Kerlikowske K. High mammographic breast density is independent predictor of local but not distant recurrence after lumpectomy and radiotherapy for invasive breast cancer. Int J Radiat Oncol, Biol, Phys 2009;73:75–9.
23. Goodwin PJ, Ennis M, Pritchard KI, Trudeau ME, Koo J, Taylor SK, et al. Insulin- and obesity-related variables in early-stage breast cancer: correlations and time course of prognostic associations. J Clin Oncol 2012;30:164–71.
24. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. Stat Methods Med Res 2007;16: 219–42.
25. Raghunathan TW, Lepkowski JM, Van Hoewyk J, Solenbeger P. A multivariate technique for multiply imputing missing values using a sequence of regression models. Surv Methodol 2001;27:85–95.
26. Rubin DB. Multiple imputation for non-response in surveys. New York: John Wiley & Sons; 1987.
27. Kerlikowske K, Walker R, Miglioretti DL, Desai A, Ballard-Barbash R, Buist DS. Obesity, mammography use and accuracy, and advanced breast cancer risk. J Natl Cancer Inst 2008;100:1724–33.
28. Arasu VA, Joe BN, Lvoff NM, Leung JW, Brenner RJ, Flowers CI, et al. Benefit of semiannual ipsilateral mammographic surveillance following breast conservation therapy. Radiology 2012;264:371–7.
29. U.S.Preventive Services Task Force. Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: recommendation statement. Ann Int Med 2005;143:355–61.
30. Rockhill B, Spiegelman D, Byrne C, Hunter DJ, Colditz GA. Validation of the Gail et al. model of breast cancer risk prediction and implications for chemoprevention. J Natl Cancer Inst 2001;93:358–66.

Published OnlineFirst March 19, 2013; DOI: 10.1158/1055-9965.EPI-12-1208-T

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association for Cancer Research

Risk Factors for Second Screen-Detected or Interval Breast Cancers in Women with a Personal History of Breast Cancer Participating in Mammography Screening

Nehmat Houssami, Linn A. Abraham, Karla Kerlikowske, et al.

Cancer Epidemiol Biomarkers Prev 2013;22:946-961. Published OnlineFirst March 19, 2013.