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Authors

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

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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**[7,2]

[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, WA

[3]Departments of Medicine and Epidemiology and Biostatistics, University of California, San Francisco, CA

[4]General Internal Medicine Section, Department of Veterans Affairs, University of California, San Francisco, CA

[5]Departments of Epidemiology and Health Services, University of Washington, Seattle, WA

[6]Institute for Technology Assessment, Department of Radiology, Massachusetts General Hospital, Boston, MA

[7]Division of Biostatistics, Department of Public Health Sciences, University of California, Davis, WA

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 (BC) within one year of screening in PHBC women.

Methods—Screening mammograms from women with history of early-stage BC 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 BC were modeled using multinomial logistic regression for *three outcomes* (screen-detected invasive BC, interval invasive BC, or DCIS) *relative to no second BC*.

Results—There were 697 second BCs, 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 BC surgery predicted all three second BC outcomes ($p<0.001$), and high odds ratios for second BCs (between 1.95 and 4.82) were estimated for breast conservation *without* radiation (relative to mastectomy). In women with *invasive* first BC, 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 BC, first BC stage, and adjuvant systemic therapy for first BC; and risk of *interval invasive* BC was highest in women <40 years at first BC (OR=3.41;1.34–

Corresponding Author: Nehmat Houssami, Screening and Test Evaluation Program, School of Public Health (A27), Sydney Medical School, University of Sydney, NSW 2006, Australia., Phone +61 (0) 419 273510; Fax +61 (0) 2 9705 1046; nehmath@med.usyd.edu.au.

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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 BC is modest, our models identify risk factors for interval second BC 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.

Keywords

Interval cancer; mammography; screening; risk factors; personal history of breast cancer

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 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 BC. Risk factor models for BC 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 BC (17, 18). Five-year risk for second BC 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 BC that elucidate *interval cancer* risk factors in PHBC women participating in mammography screening. Because second BC 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 BC 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 BC in PHBC women (13, 19) and therefore interval cancers may be associated with different outcomes.

We therefore aimed to develop multivariable models that identify independent risk factors for a second (ipsilateral *or* contralateral) BC within one year of screening mammography in

women with a PHBC. We examined the risk of the second BC 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 five 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 BC 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 perform 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 BC (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 time-frame and included 1863 more PHBC women than the previously evaluated cohort. Cancer registry and pathology databases were used to ascertain whether a woman had a subsequent BC 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 & mammogram characteristics

Age, self-reported race/ethnicity, first-degree family history of BC, menopausal status, time since last mammogram (prior to 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 & follow-up for second breast cancers

Time since first cancer was the difference between the screening mammogram date and the date of first BC 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 six months of initial diagnosis. For missing cancer registry surgery information, self-reported mastectomy and lumpectomy history (collected within 18 months after diagnosis and prior to second BC diagnosis) was used. Screening mammograms were considered to be associated with an outcome of a *second BC* (in-breast recurrence or second ipsilateral or contralateral BC) if DCIS or invasive BC were observed within one year of that screen or prior to the next screen if it occurred within 9 to 12 months after the screen. If a second BC outcome was observed during follow-up after a negative mammogram, this was considered a false negative screen and defined an interval (second) BC.

Statistical Analysis

Frequency distributions of screens and cancers were computed for demographic, mammogram, and first cancer characteristics. Cancer rates per 1000 screens and 95% confidence intervals (CI) were calculated. Using multinomial logistic regression, we examined the association between each variable and the probability (odds ratio (OR)) of a second BC using joint modeling for *three* outcomes (screen-detected invasive BC, interval invasive BC, or DCIS) whereby the OR for each outcome was estimated relative to that of *not having a second BC* (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 performed separately in PHBC women with DCIS *first* cancer and those with invasive *first* cancer given that some variables (for example, node status, chemotherapy) do not apply to, or would be infrequently reported in, those with DCIS history : variables found to be associated with BC risk (based on *global* $P < 0.05$ for joint modeling for three outcomes) in univariate models were entered into a multivariable model for each group defined by first BC type; breast density and BMI were also included based on prior knowledge of their association with second BC 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 performed 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 to *screen-detected* invasive BC, relative to no second BC during follow-up.

To evaluate model fit, receiver operating characteristic (ROC) curves and areas under the curves (AUCs) were computed based on logistic regression models that were performed for each outcome (screen-detected or interval invasive BC, or DCIS) relative to no second cancer. AUCs were averaged over the ten imputations to obtain an overall AUC. The AUCs and standard errors 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 BC diagnosis within one year of mammography. Thus, women only contributed observations up until the time they were diagnosed with a second BC. 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 BC, 177 DCIS) occurred within 12 months of screening; of these 240 were interval cancers (206 invasive BC, 34 DCIS). Cancer rates *per 1000* screens (95%CI) were: overall cancer rates 10.3/1000 (9.5–11.1), invasive BC 7.7/1000 (7.0–8.4), DCIS 2.6/1000 (2.2–3.0), interval BC 3.5/1000 (3.1–4.0), and *interval* invasive BC 3.0/1000 (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 BC, among women with *DCIS first* cancer. Significant variables were age at mammography, first degree family history of BC, 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* BC. Significant variables were age at mammography, first-degree family history of BC,

menopausal status, breast density, time since last mammogram, time since first BC, first cancer mode of detection, age at first BC, stage of first BC, primary surgery, and adjuvant systemic therapy. Significant variables were carried forward into multivariable models, with the exception of the two (correlated) age variables for which only age at first BC was considered. For women with an invasive first BC, 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 BC surgical treatment (with/out radiation) was associated with all three 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 BC (OR=2.14) or interval invasive BC (OR=3.06), and BMI was associated with increased risk of screen-detected invasive second BC (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 BC significantly differed. The estimated AUCs (95% CIs) for screen-detected invasive BC, interval invasive BC, and DCIS (versus 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 remained significantly associated with outcomes: first degree family history of BC ($p=0.021$), breast density ($p=0.016$), time since last mammogram ($p=0.048$), age at first BC ($p=0.023$), stage of first BC ($p=0.032$), primary surgery ($p<0.001$), and adjuvant systemic therapy ($p=0.019$). Relative to screens in women who had mastectomy for first BC, screens in those who had breast conservation had increased odds of screen-detected or interval invasive BC 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 BC and for DCIS. Age <40 years at first BC, breast density (BI-RADS 'extremely dense'), and first degree family history of BC significantly increased the odds of an *interval* invasive BC (Table 5). Time since last mammogram (15+ months) increased the odds of screen-detected invasive BC (OR=1.59); first cancer stage (IIB) increased the odds of DCIS (OR=2.46). Although time since the first BC was weakly associated with outcomes in the multivariable model ($p=0.06$), screens in women with ≥7 years (referent 1–2 years) from first BC had higher odds of screen-detected invasive BC or DCIS. In this model, the odds of an *interval* invasive BC was significantly higher than the odds of screen-detected invasive BC ($p=0.035$), relative to no second BC, in women with extremely dense breasts. There was no evidence that the odds of an interval versus screen-detected invasive BC, relative to no second BC, 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 BC diagnosis was significantly associated with risk of an *interval* invasive BC 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 fibro-glandular tissue also had lower risk of an *interval* invasive BC (OR=0.39 (0.21–0.72)). Based on the final model for women with invasive *first* cancer (Table 5), estimated AUCs (95% CIs) for screen-detected invasive BC, interval invasive BC, 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 BC (ipsilateral breast recurrence or second cancer in either breast) in PHBC women who participated in mammography screening, and report risk factors for *interval* invasive BC. 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 BC 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 10.3/1000 screens within one year of screening, with an invasive BC rate of 7.7/1000 screens. The *interval invasive* BC rate was 3.0/1000 screens within one year of mammography demonstrating that PHBC women are at increased risk of an *interval invasive* BC.

Our multivariable models make a new contribution to existing knowledge on the risk of second BC by highlighting factors that predict the likelihood of a screen-detected invasive *or* an interval invasive (second) BC *or* DCIS within 1 year of receiving screening mammography. Distinction between these three outcomes is relevant for follow-up care of PHBC women in whom risk factors for second BCs 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 BC because factors increasing the risk of screen-detected second BC are effectively 'managed' through mammography screening. Our work, therefore, addresses the gap in knowledge regarding risk factors that render mammography screening less sensitive in PHBC women and increase the odds of an interval invasive BC among screened women. Furthermore, most studies reporting on second BC in the context of PHBC women participating in screening (2–4, 11, 28) have considered either ipsilateral *or* contralateral second BC (and not both), have not estimated interval cancer rates or risk of interval second BC, 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 et al (19) is the only study to have examined second BC risk in PHBC women participating in screening using multivariable analysis, however it considered overall risk of a second BC, whereas we specifically examined the three defined second BC outcomes. Although variables increasing the overall risk of a second BC would be expected to increase the risk of screen-detected or interval second BC, for the reasons outlined above we aimed to address the evidence-gap on risk factors for interval second BC.

In women with *DCIS first* cancer (Table 4), the dominant factor driving risk of another BC was surgical treatment (with/out radiation) received for first BC, which was significantly associated with *all* modeled outcomes. Although the risk of another BC depends on the number of 'breasts at risk' (hence unilateral mastectomy would approximately halve the risk of another BC), and also evidenced in the higher underlying BC rates in PHBC women who had initial breast conservation (Table 1), we found that screens of women who had breast conservation without radiation had over 4 times increased risk of screen-detected or interval invasive second BC. The finding that women aged 70–79 years with a history of DCIS had increased risk for both screen-detected invasive BC and interval invasive BC (relative to the younger referent age-group, Table 4) indicates a higher underlying risk in this age-group and suggests an age-related biological basis for increased risk of developing invasive BC in women with DCIS first cancer.

The model in women with *invasive first* BC (Table 5) highlighted that risk in this group was relatively complex and driven by several factors, including first BC 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 BC were younger age at first BC diagnosis, 'extremely dense' breasts, first degree BC family history, and breast conservation (with/out radiation). In women with an *invasive* first BC (Table 5) adjuvant endocrine therapy predicted reduced risk of screen-detected second BC and of DCIS; chemotherapy alone was not significantly associated with risk. Systemic therapy of any type did not affect the risk of an *interval* BC. Fatty (relative to dense) breasts predicted reduced risk of DCIS and of an interval invasive BC in women with an invasive first BC. Although we cannot explain the finding that first BC stage (IIB) had higher odds of DCIS as the second BC, we noted that a relatively high proportion of women with stage IIB first 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 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 BC risk but also on the woman's absolute risk of developing a second BC, her life-expectancy, and first BC-related prognosis. Our results for *interval* invasive BC can however guide adjunct screening research by targeting PHBC women at increased risk of interval BC, for example those who received breast conservation without radiation. Other specific groups at ≥2 times increased risk of an *interval* invasive BC were 70–79 year olds with history of DCIS, and women with invasive first BC who had extremely dense breasts *or* who were <40 years at first BC diagnosis – although OR estimates varied depending on the referent category, there was consistent evidence of increased risk of an interval BC in women <40 years at first BC diagnosis. It is likely that this partly reflects women with hereditary risk and/or BC susceptibility genes (although we did not have the data to investigate this) and reinforces the recommendation to consider genetic counseling in women diagnosed with BC 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, since they had one breast at risk: this should *not* be a reason to preferentially recommend mastectomy for BC 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 one year of screening) the finding that local treatment received for first BC 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 BC *or* DCIS in PHBC women, so we cannot compare the results of our models and their accuracy to other research. However, we estimated that our models had moderate accuracy (AUCs 0.67 to 0.73) with similar accuracy to BC 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 BC 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 BC 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 versus 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 BC including risk factors for interval invasive BC in PHBC women who had undergone mammography screening. Although the risk of a second BC 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 BCs 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 BC to guide formal evaluations to determine whether tailored breast screening reduces the interval BC rate in PHBC women.

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Table 1

Distribution of variables, number of cancers*, and cancer rates in women with a personal history of breast cancer (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 1000 screens (95% CI)	Invasive cancer rate per 1000 screens (95% CI)	Interval cancer rate per 1000 screens (95% CI)	Invasive interval cancer rate per 1000 screens (95% CI)
All screening mammograms	***67819***	***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, years							
< 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	6925(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	16998(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	17326(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	17195(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+	8560(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	55444(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	2370(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	4820(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	1206(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	1388(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	43597(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	13409(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-	4054(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	54471(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	4104(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)

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 1000 screens (95% CI)	Invasive cancer rate per 1000 screens (95% CI)	Interval cancer rate per 1000 screens (95% CI)	Invasive interval cancer rate per 1000 screens (95% CI)
2 - Scattered fibroglandular tissue	25806(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	21221(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	2920(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)
BMI (32.2%)[£]							
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)	19803(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)	15033(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)	6767(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+)	3594(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[§] **(1.8%)**							
9–14 months	55354(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 months	8350(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+ months	2900(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	61514(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	6288(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 year (6–11 months)	4762(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 years	15486(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 years	15988(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 years	12469(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 years	11562(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 years	7552(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	26429(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	4346(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)

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 1000 screens (95% CI)	Invasive cancer rate per 1000 screens (95% CI)	Interval cancer rate per 1000 screens (95% CI)	Invasive interval cancer rate per 1000 screens (95% CI)
clinical/diagnostic detected	8238(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	2578(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, years							
< 40	2701(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	13688(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	18192(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	17411(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	12649(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+	3178(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)
Type of first breast cancer							
Ductal carcinoma in situ (DCIS)	13958(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	53861(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	13958(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	32607(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	15405(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	5849(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 [†]							
no metastases	41764(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	12097(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[‡] **(55.9%)**							
Grade I	1134(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	2163(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	2853(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 [†] **(18.2%)**							
Grade I	10287(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)

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 1000 screens (95% CI)	Invasive cancer rate per 1000 screens (95% CI)	Interval cancer rate per 1000 screens (95% CI)	Invasive interval cancer rate per 1000 screens (95% CI)
Grade II	18863(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	14891(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[ǂ] (88.0%)							
ER+ or PR+	1328(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[†] (21.0%)							
ER+ or PR+	35870(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−	6689(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	24146(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	32501(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	8912(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)
Radiation therapy (4.8%)							
None	29025(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	35524(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	31990(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[**]	16085(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	8956(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	6360(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%)[£]							
No	46367(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	3172(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)

[*] 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

[£] one site was removed from each of these variables due to high proportion of missing values at that site

§ Refers to any (screening or diagnostic) mammogram only in calculation of time since last mammogram

† based on women with a prior history of invasive breast cancer

‡ based on women with a prior history of DCIS

** includes 19 women with a prior history of DCIS who reportedly had chemotherapy (12 with chemotherapy only; 7 with both endocrine and chemotherapy)

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 BC**	**Interval *invasive* BC**	**DCIS second BC**	
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**p-value†**
Age at mammography, years				
<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%)**				
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 months	Referent	referent	Referent	0.58
15–23 months	0.96 (0.49, 1.89)	0.75 (0.26, 2.13)	0.95 (0.45, 2.01)	
24+ months	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

Variable (proportion missing data for variable where applicable)	**Screen-detected *invasive* second BC**	**Interval *invasive* BC**	**DCIS second BC**	
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**p-value†**
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 year (6–11 months)	1.22 (0.34, 4.47)	0.64 (0.14, 2.89)	1.43 (0.51, 4.04)	0.66
1–2 years	Referent	referent	Referent	
3–4 years	1.53 (0.70, 3.35)	0.76 (0.33, 1.76)	1.35 (0.66, 2.74)	
5–6 years	**2.62 (1.24, 5.53)**	0.80 (0.32, 1.95)	1.32 (0.62, 2.82)	
7–9 years	1.66 (0.73, 3.76)	0.67 (0.25, 1.81)	1.05 (0.46, 2.42)	
≥ 10 years	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)	
Age at first breast cancer, years				
< 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 ††	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%) **				
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)	

* Each univariate model included the variable of interest and was adjusted for mammography registry and primary surgery received for first breast cancer

† P is the global p-value for each univariate analysis in which joint modeling was performed for the three outcomes (screen-detected or interval invasive, or DCIS, second breast cancer) with no cancer as the referent category.

** 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)

†† includes 19 women with a prior history of DCIS who reportedly had chemotherapy (12 with chemotherapy only; 7 with both endocrine and chemotherapy)

OR and P values shown in bold indicate statistically significant association

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 BC	Interval *invasive* BC	DCIS second BC	
	OR (95% CI)	OR (95% CI)	OR (95% CI)	p-value†
Age at mammography, years				
<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%) **				
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 months	referent	Referent	referent	**0.018**
15–23 months	1.44 (0.98, 2.11)	1.05 (0.64, 1.7)	0.82 (0.41, 1.65)	
24+ months	**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

Variable (proportion missing data where applicable)	Screen-detected *invasive* second BC	Interval *invasive* BC	DCIS second BC	
	OR (95% CI)	OR (95% CI)	OR (95% CI)	p-value†
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 year (6–11 months)	0.78 (0.39, 1.56)	1.00 (0.52, 1.92)	**2.19 (1.01, 4.72)**	**0.036**
1–2 years	referent	Referent	referent	
3–4 years	0.78 (0.50, 1.23)	0.95 (0.60, 1.49)	1.02 (0.51, 2.02)	
5–6 years	1.26 (0.82, 1.92)	0.81 (0.49, 1.34)	0.98 (0.47, 2.05)	
7–9 years	1.36 (0.89, 2.08)	0.99 (0.61, 1.62)	1.77 (0.92, 3.38)	
≥ 10 years	**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)	
Age at first breast cancer, years				
< 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)**	

Variable (proportion missing data where applicable)	Screen-detected *invasive* second BC	Interval *invasive* BC	DCIS second BC	
	OR (95% CI)	OR (95% CI)	OR (95% CI)	p-value†
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%)**				
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)	

*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

†P is the global p-value for each univariate analysis in which joint modeling was performed for the three outcomes (screen-detected or interval invasive, or DCIS, second breast cancer) with no cancer as the referent category.

**one site was removed due to high proportion of missing values for variable at that site

OR and P values shown in bold indicate statistically significant association

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 BC	Interval *invasive* BC	DCIS second BC	
	OR (95% CI)	OR (95% CI)	OR (95% CI)	p-value†
Age at mammography, years				
<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§	0.36 (0.11, 1.16)	1.60 (0.65, 3.95)	0.40 (0.12, 1.28)	

*Model also adjusted for mammography registry (screens from one site were removed from model due to high proportion of missing values for BMI).

†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.

§includes 19 women with a history of DCIS who reportedly had chemotherapy (12 with chemotherapy only; 7 with both endocrine and chemotherapy)

OR and P values shown in bold indicate statistically significant association

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 BC	Interval *invasive* BC	DCIS second BC	
	OR (95% CI)	OR (95% CI)	OR (95% CI)	p-value†
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 months	referent	referent	referent	**0.048**
15+ months	**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 year (6–11 months)	1.34 (0.71, 2.55)	1.01 (0.51, 2.00)	1.92 (0.89, 4.13)	0.060
1–2 years	referent	referent	referent	
3–4 years	0.84 (0.52, 1.37)	0.91 (0.56, 1.46)	1.06 (0.54, 2.07)	
5–6 years	1.43 (0.92, 2.25)	0.78 (0.46, 1.33)	0.86 (0.40, 1.86)	
7+ years	**1.52 (1.00, 2.32)**	0.98 (0.61, 1.57)	**1.87 (1.01, 3.49)**	
Age at first breast cancer, years				
< 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				

Variable	Screen-detected *invasive* second BC	Interval *invasive* BC	DCIS second BC	
	OR (95% CI)	OR (95% CI)	OR (95% CI)	p-value†
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)**	

*Model also adjusted for mammography registry (screens from one site were removed from model due to high proportion of missing values for BMI)

†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.

OR and P values shown in bold indicate statistically significant association