Factors associated with being diagnosed with high severity of breast cancer: a population-based study in Queensland, Australia

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Abstract

Purpose: This study explores factors that are associated with the severity of breast cancer (BC) at diagnosis.

Methods: Interviews were conducted among women (n=3,326) aged 20-79 diagnosed with BC between 2011-2013 in Queensland, Australia. High-severity cancers were defined as either Stage II-IV, Grade 3, or having negative hormone receptors at diagnosis. Logistic regression models were used to estimate odds ratios (ORs) of high severity BC for variables relating to screening, lifestyle, reproductive habits, family history, socioeconomic status, and area disadvantage.

Results: Symptom-detected women had greater odds (OR=3.38, 2.86-4.00) of being diagnosed with high-severity cancer than screen-detected women. Women who did not have regular mammograms had greater odds (OR=1.78, 1.40-2.28) of being diagnosed with high-severity cancer than those who had mammograms biennially. This trend was significant in both screen-detected and symptom-detected women. Screen-detected women who were non-smokers (OR=1.77, 1.16-2.71), postmenopausal (OR=2.01, 1.42-2.84), or employed (OR=1.46, 1.15-1.85) had greater odds of being diagnosed with high-severity cancer than those who were current smokers, premenopausal, or unemployed.

Symptom-detected women being overweight (OR=1.67, 1.31-2.14), postmenopausal (OR=2.01, 1.43-2.82), had hormone replacement therapy (HRT) <2 years (OR=1.60, 1.02-2.51) had greater odds of being diagnosed with high-severity cancer than those of healthy weight, premenopausal, had HRT >10 years.

Conclusion: Screen-detected women and women who had mammograms biennially had lower odds of being diagnosed with high-severity breast cancer, which highlighted the benefit of regular breast cancer screening. Women in subgroups who are more likely to have more severe cancers should be particularly encouraged to participate in regular mammography screening.

Introduction

Breast cancer (BC) survival has improved over the past decades in Australia [1,2], largely due to improvements in early detection and treatment [3]. However, those diagnosed with advanced disease still have relatively lower survival [4].

Lower survival is largely attributed to greater severity of cancer at diagnosis, including later stage, higher grade, or negative hormone receptors (HR-) [4-8]. An Australian study reported that women who lived in disadvantaged areas or areas with longer travel time to health facilities were more likely to be diagnosed with advanced BC [9]. Since most of the studies however used population-based cancer registry data, the results were restricted by the limited individual-level information available. Therefore, it remains unclear which individual-level factors are related to higher severity of BC at diagnosis in the Australian population.

International studies report that individual factors such as older age [10], obesity [11], no family history of BC [12], being unmarried [13], lower education or income [14-16] are associated with a more advanced stage at diagnosis of BC. In Australia, the *BreastScreen Program* invites women aged 50-74 to undergo free mammograms every two years, with women aged 40-49 also eligible to be screened but not actively invited [17]. In addition, women with higher risk of BC are encouraged to have an individualised surveillance program developed in consultation with their doctors [18]. While these programs should, in theory, reduce the association between individual-level socioeconomic status (SES) and severity at diagnosis, participation in these programs by Australian women in the target age group is relatively low, around 50% [19]. Therefore, the strength of the association between individual-level SES and severity at diagnosis in the Australian population remains unclear.

This study uses a large, population-based cohort of women diagnosed with BC in Queensland (Australia) to explore individual and area-level factors associated with high severity of BC at diagnosis. Identification of modifiable factors has the potential to inform interventions to reduce the likelihood of high-severity disease at diagnosis and, in doing so, improve survival and other outcomes.

Methods

Ethical approval was obtained from the Human Research Ethics Committee of Griffith University, Australia (PSY/C4/09/HREC).

Study population

The Breast Cancer Outcomes Study (BCOS) [20,21] is a longitudinal study among women aged 20 to 79 years diagnosed with invasive BC in Queensland, Australia between 1 January 2011 and 30 June 2013. In total, 5426 eligible women were identified for a telephone interview. Among these, 66 were deceased and 688 were not consented by their doctor. Of the remaining 4672 women with doctor consent, 3326 (71.2%) completed the interview. There was no evidence of a difference in age distribution between participants and non-participants ($p=0.33$), however women living in major cities ($p=0.04$) and diagnosed with advanced disease ($p=0.03$) were less likely to participate. More details on study population and recruitment can be found in a previous publication [21].

Data collection

Full details of data collection have been described previously [20,21]. Briefly, a validated, semi-structured telephone interview administered by trained health interviewers was used to collect details such as each women's pathway to diagnosis, socio-demographic information and medical history, with additional clinical information extracted from medical records. The telephone interview was conducted prior to the completion of the self-administered questionnaire. These were completed within three years after diagnosis, with half of the participants returning their questionnaire within 391 days (time interval between diagnosis and the returning of self-administered questionnaire ranged from 93 to 923 days, interquartile range from 276 to 890 days) (Supplementary Figure 1).

Participants were classified into two groups: symptom detected and screen detected. Those detected by symptoms were women whose first sign or symptom of BC was initially noticed by themselves, a doctor, or a layperson. The screen detected group represented women where the suspicion of BC was made via routine mammography or ultrasound [21].

Individual-level information

Individual-level information were collected about the time before diagnosis (Table 1) including frequency of having mammograms, lifestyle (such as BMI, physical activity), reproductive history (such as age at menarche, menopause status), family history of breast and ovarian cancer, SES (such as education, employment, gross household income, health insurance status), and residential location. In Australia, individuals who pay for private health insurance avoid the typically longer waiting times associated with treatment in the public hospital system and have their choice of treating doctors [22].

Clinical coders extracted relevant data items from histopathology reports including age at diagnosis, tumour site and size, morphology, histological grade, degree of lymph node involvement, estrogen, progesterone and Herceptin status. Cancer stage was assigned by the clinical coders according to the current American Joint Committee Cancer Staging Manual at time of coding [23].

Area-level information

The geographical unit of analysis was the Statistical Area Level 2 (SA2), as defined by the 2011 Australian Statistical Geography Standard (ASGS) classification system [20]. The SA2s were designed to be relatively homogeneous in terms of the socioeconomic characteristics of the populations they contain [20].

Each participant was assigned to an SA2 based on their residential address at cancer diagnosis. Area-level factors were geographic remoteness, accessibility to treatment, and area-level SES (Table 1). Remoteness was designated using the ASGS Remoteness Areas [24]. Four categories of remoteness (“Major city”, “Inner regional”, “Outer regional” and “Remote/very remote”) were determined by access to services. We combined the categories “Outer regional” and “Remote/very remote” to allow sufficient numbers for analyses. Accessibility to treatment was classified based on the road travel time from their residential SA2 to the closest radiation facility (high: <1 h, low $\geq$ 1 h) [25]. Area-level SES was measured using the 2011 Index of Relative Socioeconomic Disadvantage (IRSD), a census-based aggregated measure that summarises information about the economic and social conditions of people and households within a SA2 [21]. While the IRSD is normally reported in Quintiles, for this study the quintiles were collapsed into three groups as ‘most

disadvantaged (Quintile 1)', 'middle SES (Quintile 2-4)', and 'least disadvantaged (Quintile 5)', to increase the numbers in each category.

Outcome measures

Three histopathological factors associated with BC survival [4-8] were selected to represent the severity of BC at diagnosis including stage, grade, and hormone receptors status. We recategorized the stage outcome into two categories (stage I or stage II-IV) to ensure enough observations for analysis. For the same reason, we also recategorized the grade outcome into two categories (Grade 1-2 or Grade 3). Previous studies have suggested that women with BC with both estrogen receptor negative (ER-) and progesterone receptor negative (PR-) had lower survival [26,27]. Therefore, the hormone receptors status outcome was categorised as hormone receptor negative (HR-, neither of the hormone receptors positive) or hormone receptor positive (HR+, with one or both the hormone receptors positive).

Since the three outcome variables were correlated, with the Pearson correlation between hormone receptors status and grade being 0.43, stage and grade being 0.23, we generated a new outcome representing the overall severity of BC at diagnosis by combining the three outcome variables. The overall severity outcome was categorised into high severity and low severity, with high severity cancers representing those diagnosed with either stage II-IV, Grade 3, or HR- cancer; and low severity cancers being those diagnosed with stage I, grade 1-2 and HR+ cancer.

Statistical analysis

While the hierarchical structure of the data (individual level and area level) suggested a multilevel model, our initial analysis using a multilevel logistic regression on the binary outcome variables showed that the variance of the random intercept at the SA2 level was almost zero. This suggested all the geographic variations of the outcome variable was accounted for by the fixed effects, the multilevel model gave the same result as an individual level model. Therefore, we used individual-level logistic regression models for the four outcome variables.

Logistic regression models were developed for each of the outcome variables including stage (Model 1), grade (Model 2), hormone receptors status (Model 3), and the overall severity (Model 4) to determine the factors associated with each outcome. All the models were adjusted for age and method of detection. For the overall severity outcome, another two

models stratified by the methods of detection (Model 5 (screen detected) & 6 (symptoms detected)) were developed to see if the influential factors for the overall severity outcome were different between symptom-detected and screen-detected women. In addition, a further analysis stratified the screen-detected women into those screened in public facilities (Model 7) and those screened in private facilities (Model 8) were conducted for the overall severity outcome.

The models were developed using a backward stepwise method [28]. All the available factors (listed in Table 1) were included in the model initially. A likelihood ratio test was used to drop variables with a p-value >0.2 . At each step, variables previously removed from the model were tested to gauge their eligibility to be re-included into the model.

Multiple imputation

Missing data ranged from 0-11.7% for predictor or outcome variables (Table 1), and a complete case analysis would have excluded 34% of the initial cohort, potentially introducing a bias if the excluded cases were a non-random sample. Missing data were handled with multiple imputation methods [29], using the *mi impute chained* and *mi estimate* commands for chained equations and subsequent regression model estimation. In the imputation modelling we included auxiliary variables that are correlated with missing variables (Pearson correlation > 0.4). All variables included in the final models were also included in the series of chained imputation equations. We used 34 imputations based on the percentage of incomplete cases [30].

All statistical analyses were performed using Stata/SE version 16 (StataCorp, TX, USA).

Results

Among the 3326 participants who completed the interview, 59 did not have stage information, 45 did not have grade, and 106 did not have hormone receptors status, resulting in 167 for whom severity could not be determined. Among those women who had values for the outcome variables, 1666 (51.0%, n=3267) were diagnosed with stage II-IV BC, 1076 (32.8%, n=3281) were grade 3 cancer, 439 (13.6%, n=3220) were HR-, and 1981 (62.7%, n=3159) were categorised as having high severity cancer (Table 1).

Stage, grade, and hormone receptors

Women whose BC was detected by symptoms were associated with 3.63 times higher odds of being diagnosed with stage II-IV BC, 2.25 times higher odds of being diagnosed with grade 3 cancer, and 2.42 times higher odds of being diagnosed with HR- cancer than those detected by screening (Table 2). Those who were diagnosed before 50 years of age were more likely to have stage II-IV and grade 3 cancer than those diagnosed after 70.

The other factors significantly associated with each of stage, grade, and hormone receptor status were similar with consistent patterns (Table 2). For the stage outcome, women who did not have biennial screening mammograms, were overweight, never smoked, postmenopausal, or not fully insured had higher odds of being diagnosed with stage II-IV cancers. For the grade outcome, not having mammograms biennially, never having smoked, duration of menstruation ≤ 35 years, postmenopausal, duration of contraceptives use ≥ 2 years, no first-degree family history of breast or ovarian cancer, or lived in inner regional areas had higher odds of being diagnosed with grade 3 BC. For the hormone receptors status outcome, higher odds of being diagnosed with HR-cancer was observed for women who never smoked and whose duration of menstruation was ≤ 35 years.

Overall severity

Women with symptom-detected BC were associated with 3.38 times higher odds of being diagnosed with high severity BC than those detected by screening (Figure 1). Not having mammograms biennially, younger age, being overweight, never having smoked, being postmenopausal, or not being fully privately insured were associated with greater odds of high severity cancer at diagnosis (Figure 1).

When stratified by methods of detection, around 40%-50% of the screen-detected women were diagnosed with high severity cancer, while the corresponding numbers for the symptom-detected women were around 70%-80% (Table 3). Although screen-detected and symptom-detected women had different proportions of high severity cancer, the magnitude and direction of the covariate effects were largely the same for most variables except employment status (Figure 1 & Table 3). For screen-detected cancers, women who were employed had greater odds of being diagnosed with high severity cancer; while for symptom-detected cancers, women who were employed tended to have lower odds of being diagnosed with high severity cancer (Figure 1 & Table 3).

Further stratification of the screen-detected women into those screened in public facilities (n=1233) and those screened in private facilities (n=409) (Supplementary Table 1) showed that among those screened in private facilities, employed women had greater odds of being diagnosed with high severity cancer than the unemployed (OR=2.24, $p<0.01$), and women not fully covered by private insurance were more likely to be diagnosed with high severity cancer than those fully insured (OR=2.10, $p=0.01$). However, there was no significant evidence of independent effects of employment status (OR=1.29, $p=0.07$) and insurance status (OR=1.09, $p=0.50$) among women who did their screening in public facilities.

Discussion

This study identified several individual and geographic factors associated with greater odds of being diagnosed with high severity BC. Women with screen-detected BC were less likely to be diagnosed with high severity cancer than those with symptom-detected BC. After adjusting for the method of detection, women who did not have regular mammograms had greater odds of being diagnosed with high severity cancer than those who had biennial mammograms. In addition, most of the factors associated with a higher risk of being diagnosed with breast cancer were associated with lower odds of being diagnosed with a high severity BC. Except for employment status, the direction and strength of the associations were similar between screen-detected and symptom-detected women.

Screen-detected women who were employed had 46% greater odds of being diagnosed with high severity cancer. The findings were independent of age at diagnosis. Possible explanations might include unmeasured barriers making it difficult for employed women to get mammograms in time and/or causing delays in definitive diagnosis after mammograms. Australian studies have reported employed migrants had lower annual clinical breast examination than unemployed migrants [31], and women with more time pressure were less likely to have mammograms than those with less time pressure [32]. However, since our model adjusted for the frequency of mammography screening, the potential barriers of getting mammograms among employed women might not be their main reason for having more severe cancer than the unemployed.

When stratifying the screen-detected women by public or private screening facilities, the employment effect was only visible among those screened in private facilities, while the

effect was not significant among women whose mammogram was in a public facility. Further exploration of this counter intuitive result is warranted.

Lower individual- or area-level SES has been linked to poorer BC survival in different countries [33-38] including Australia [39]. Studies have attributed this finding to more advanced stages of cancers at diagnosis and more limited treatment, with suggested reasons varying with the country and health system characteristics [40-44]. In Australia, as in our study, women from more disadvantaged areas have been shown to be more likely to be diagnosed with advanced BC [9] while other Australian studies have shown they also have less access to specialists and received suboptimal treatments [44,45].

In terms of individual-level SES, we found that except for employment status, there was no evidence that other SES factors such as education, insurance status, income, number of cars, marital status, and language spoken at home having a significant independent association with severity at diagnosis. Apart from employment status, the lack of significant associations with SES among screen-detected participants may reflect the impact of the *BreastScreen Program* in providing free access to mammography screening for all Australian women aged 50-74 years [46], along with BC awareness campaigns [47,48]. The results suggested that in Australia, the influence of individual SES on BC survival [49] might be less attributable to pre-diagnosis factors but mainly attributable to post-diagnosis factors such as the period between diagnosis and treatment or different treatment options.

Women with higher SES have been reported to have higher incidence of HR+ subtypes of breast cancer compared with lower SES, possibly related to the higher levels of circulatory hormones as a result of their predominant reproductive patterns such as earlier menarche, lower parity and later age at first birth [50-52]. However, we did not find a strong association between hormone receptor status at diagnosis and SES factors.

We found that most of the established risk factors for being diagnosed with BC such as older age, smoking, longer duration of menstruation, use of HRT, and family history of breast and ovarian cancer [53-56] were associated with a lower odds of being diagnosed with high severity BC. Some of this might be explained by a higher awareness of BC among high-risk participants. For example, an Australian study reported that women with a family history of BC were more likely to overestimate their risk of having BC [57], and screening participation rates are reported to be higher among older women than younger women [19]. However, the

higher severity among younger patients may also be a function of tumour biology, in that while younger women have a lower incidence of BC, they are also more likely to have more aggressive tumours [58] and less likely to be detected early due to their higher breast density [59]. Even though population-based mammography screening is not recommended for younger women, alternative methods of identifying these cancers earlier including conducting breast self-examination monthly and clinical breast examination yearly by family physician [32] should be encouraged especially among subgroups with higher odds of being diagnosed with high severity cancer.

It is likely that at least some of the differential in severity between screen-detected and symptom-detected cancers is due to the propensity for length-time bias and overdiagnosis associated with mammography screening [60]. Since women were screened at a certain point in time, those with slow-growing (low severity) disease were more likely to be detected by screening while more aggressive (high severity) cancers tend to be detected after having symptoms (length-time bias) during the screening intervals [61]. Length-time bias is related to overdiagnosis, as screening tends to detect slower-growing cancers that would never have caused harm to the patients had they remained undetected [62]. However, it is also reasonable to suggest that the likelihood of length-time bias and overdiagnosis would be consistent within each of the screen-detected and symptom-detected cohort, providing greater confidence that the differences observed within each of these strata reflect true differences.

Study strengths include the use of a large cohort of women ascertained through a population-based cancer registry, which may strengthen the potential generalizability of the findings. In addition, the use of individual level variables which are not available in cancer registry data enables us to explore the association between area SES and individual factors simultaneously. Further, participants were stratified by detection method and thus the different impacts of the influential factors on the severity of BC detected by screening or symptoms were elucidated. Further, multiple imputation was used to enable all participants to be included into the final analysis, thus reducing the potential for additional biases by excluding records with missing data.

The retrospective nature of this study increases the potential for inaccuracies in how information such as reproductive history behaviours were provided. In order to evaluate the accuracy of the information, respondents were asked “How accurate is this age?” after questions like “At what age did you first get your periods?”. From these data, more than 95%

of participants were confident about their menstruation history; more than 90% of participants stated the accuracy for their contraceptive use history was within two years; and more than 85% stated that the accuracy of their HRT histories was within two years.

Conclusion

This study identified important factors associated with being diagnosed with high severity BC. Although the screening-related biases should be considered, the significantly lower odds of screen-detected cancers being more severe, and the lower odds of women who have regular mammograms being diagnosed with more severe cancers, supports the effective role of regular screening in early detection. The finding of a greater odds of high severity BC among screen-detected women who were employed requires further investigation. Women in population subgroups that are more likely to have higher proportion of severe cancers should be particularly encouraged to participate in mammography screening.

Table 1 Observed percentages of breast cancer diagnosed with late stage, high grade, negative hormone receptors, or overall high severity by different factors.

	No. women (%)	Percentages (95% CI ¹)			
		Stage II-IV ²	Grade 3 ³	HR- ⁴	High severity ⁵
All	3,326 (100)	51.0 (49.3-52.7)	32.8 (31.2-34.4)	13.6 (12.4-14.8)	62.7 (61.0-64.4)
Method of detection					
Screening	1,642 (49.4)	33.8 (31.5-36.1)	22.5 (20.5-24.5)	8.7 (7.4-10.1)	47.5 (45.0-49.9)
Symptoms	1,684 (50.6)	68.3 (66.0-70.5)	43.0 (40.6-45.4)	18.5 (16.6-20.4)	78.2 (76.1-80.2)
Frequency of screening					
At least two-yearly	2,276 (68.4)	43.2 (41.2-45.3)	28.6 (26.7-30.4)	13.0 (11.6-14.4)	56.0 (53.9-58.0)
Infrequently	499 (15.0)	65.8 (61.6-70.0)	39.8 (35.4-44.1)	15.6 (12.3-18.8)	76.4 (72.6-80.3)
None	549 (16.5)	70.2 (66.3-74.1)	44.2 (40.0-48.4)	14.5 (11.5-17.5)	78.9 (75.3-82.4)
Unknown	2 (0.1)	50.0 (0.0-100.0)	50.0 (0.0-100.0)	0.0 (-)	50.0 (0.0-100.0)
Age of diagnosis					
<50	897 (27.0)	60.8 (57.6-64.0)	43.0 (39.7-46.2)	15.7 (13.2-18.1)	72.5 (69.5-75.6)
50-59	946 (28.4)	52.5 (49.3-55.7)	32.5 (29.5-35.5)	14.3 (12.1-16.6)	63.9 (60.8-67.1)
60-69	1,026 (30.9)	43.3 (40.3-46.4)	26.8 (24.1-29.6)	12.1 (10.1-14.2)	55.7 (52.6-58.8)
70-79	457 (13.7)	45.9 (41.2-50.6)	26.9 (22.8-31.0)	11.6 (8.6-14.6)	56.8 (52.1-61.5)
Lifestyle					
BMI⁶					
Healthy weight	1,292 (38.9)	48.6 (45.8-51.3)	33.0 (30.5-35.6)	14.1 (12.1-16.0)	60.5 (57.8-63.2)
Overweight	2,034 (61.2)	52.5 (50.3-54.7)	32.6 (30.6-34.7)	13.4 (11.9-14.9)	64.1 (62.0-66.3)
Physical activity					
Insufficient	1,444 (43.4)	51.7 (49.1-54.3)	31.7 (29.2-34.1)	13.1 (11.3-14.9)	62.7 (60.1-65.2)
Sufficient	1,835 (55.2)	50.7 (48.4-53.0)	33.6 (31.5-35.8)	14.1 (12.5-15.7)	63.1 (60.8-65.3)
Unknown ⁷	47 (1.4)	40.4 (26.2-54.6)	34.0 (20.3-47.7)	12.8 (3.1-22.4)	51.1 (36.6-65.5)
Smoking					
Current smoker	226 (8.0)	51.5 (45.5-57.6)	31.7 (26.1-37.3)	11.9 (7.9-15.8)	63.0 (57.1-68.9)
Used to smoke	1,169 (35.2)	49.5 (46.6-52.4)	31.7 (29.0-34.4)	12.1 (10.2-14.0)	60.8 (57.9-63.7)
Never smoked	1,886 (56.7)	51.9 (49.6-54.1)	33.6 (31.5-35.8)	14.9 (13.2-16.5)	63.9 (61.6-66.1)
Unknown	5 (0.2)	40.0 (0.0-88.0)	40.0 (0.0-88.0)	0.00 (-)	60.0 (12.0-100.0)
Drinking					
<Once a month	1,293 (38.9)	52.0 (49.3-54.8)	31.3 (28.7-33.8)	13.5 (11.6-15.4)	63.0 (60.3-65.7)
≥Once a month	2,033 (61.1)	50.3 (48.2-52.5)	33.7 (31.7-35.8)	13.7 (12.2-15.2)	62.5 (60.4-64.7)
Reproductive history					
Age at menarche					
≤13	2,160 (64.9)	51.9 (49.8-54.0)	32.4 (30.4-34.4)	13.5 (12.0-14.9)	63.2 (61.2-65.3)
>13	1,131 (34.0)	49.6 (46.7-52.6)	33.6 (30.8-36.4)	14.2 (12.2-16.3)	62.0 (59.1-64.9)
Unknown	35 (1.05)	38.2 (21.7-54.8)	31.4 (15.8-47.0)	5.7 (0.0-13.5)	52.9 (35.9-70.0)
Duration of menstruation					
≤35 years	1,639 (49.3)	54.2 (51.8-56.6)	38.3 (35.9-40.7)	15.6 (13.8-17.3)	67.1 (64.7-69.4)
>35 years	1,601 (48.1)	48.2 (45.7-50.7)	27.3 (25.1-29.5)	11.8 (10.2-13.4)	58.6 (56.1-61.0)
Unknown	86 (2.6)	41.7 (31.1-52.3)	29.1 (19.4-38.7)	10.6 (4.0-17.2)	56.6 (45.9-67.4)
Menopause					
Yes	2,691 (80.9)	51.1 (49.2-53.0)	32.3 (30.5-34.0)	13.6 (12.3-14.9)	62.8 (60.9-64.6)
No	635 (19.1)	50.5 (46.6-54.4)	35.1 (31.3-38.9)	13.8 (11.1-16.5)	62.4 (58.6-66.3)
Age started using contraceptives					
Never used	413 (12.4)	48.6 (43.8-53.5)	29.3 (24.9-33.7)	11.7 (8.6-14.9)	60.4 (55.5-65.2)
≤18	1,062 (31.9)	55.5 (52.4-58.5)	39.7 (36.7-42.7)	16.2 (14.0-18.5)	67.4 (64.5-70.3)
>18	1,835 (55.2)	49.0 (46.7-51.3)	29.6 (27.5-31.7)	12.6 (11.1-14.2)	60.7 (58.4-62.9)
Unknown ⁷	16 (0.5)	40.0 (14.3-65.7)	26.7 (3.5-49.8)	6.3 (0.0-18.5)	50.0 (22.8-77.2)
Duration of using contraceptives					
Never or <2 years	688 (20.7)	49.0 (45.2-52.7)	27.3 (24.0-30.7)	11.4 (9.0-13.8)	60.6 (56.9-64.4)
2-10 years	1,301 (39.1)	51.7 (48.9-54.4)	33.4 (30.8-35.9)	14.5 (12.6-16.4)	62.4 (59.7-65.1)
>10 years	1,318 (39.6)	51.5 (48.7-54.2)	35.1 (32.6-37.7)	13.9 (12.0-15.8)	64.2 (61.6-66.9)
Unknown ⁷	19 (0.6)	44.4 (20.8-68.1)	27.8 (6.5-49.1)	15.8 (0.0-32.6)	52.9 (28.5-77.4)
Age at first childbirth					
Never give birth	112 (3.4)	47.3 (37.9-56.6)	35.1 (26.2-44.1)	16.7 (9.6-23.7)	60.4 (51.0-69.7)
≤30	2,358 (70.9)	50.4 (48.3-52.4)	32.1 (30.2-34.0)	13.9 (12.5-15.4)	62.1 (60.1-64.1)
>30	467 (14.0)	54.2 (49.7-58.8)	32.2 (27.9-36.4)	12.9 (9.8-16.0)	64.0 (59.6-68.5)
Unknown ⁷	389 (11.7)	52.0 (46.9-57.0)	36.8 (32.0-41.7)	11.8 (8.5-15.0)	65.5 (60.6-70.4)
Number of children					
None	112 (3.4)	47.3 (37.9-56.6)	35.1 (26.2-44.1)	16.7 (9.6-23.7)	60.4 (51.0-69.7)
1-2	1,554 (46.7)	50.6 (48.0-53.1)	32.8 (30.5-35.2)	14.6 (12.8-16.4)	62.3 (59.9-64.8)
>2	1,660 (49.9)	51.7 (49.2-54.1)	32.6 (30.3-34.9)	12.5 (10.9-14.1)	63.2 (60.8-65.6)

Duration of breastfeeding					
None	957 (28.8)	50.2 (47.0-53.4)	33.1 (30.1-36.0)	13.5 (11.3-15.7)	62.5 (59.4-65.7)
1-12 months	1,157 (34.8)	50.3 (47.4-53.2)	33.0 (30.3-35.7)	14.1 (12.0-16.1)	61.6 (58.7-64.5)
>12 month	1,212 (36.4)	52.3 (49.5-55.2)	32.4 (29.7-35.0)	13.3 (11.4-15.3)	63.9 (61.2-66.7)
Duration of HRT⁸					
Never or < 2 years	2,441 (73.4)	53.6 (51.6-55.6)	35.0 (33.1-36.9)	13.9 (12.5-15.3)	65.1 (63.2-67.1)
2-10 years	515 (15.5)	43.4 (39.0-47.7)	27.7 (23.8-31.6)	13.0 (10.1-16.0)	56.5 (52.1-60.9)
>10 years	290 (8.7)	42.3 (36.5-48.0)	23.1 (18.2-28.0)	10.3 (6.7-13.8)	52.3 (46.5-58.2)
Unknown ⁷	80 (2.4)	51.9 (40.8-63.0)	34.6 (24.0-45.2)	20.3 (11.3-29.2)	67.1 (56.5-77.7)
Family history					
Relatives with breast or ovarian cancer					
None	1,713 (51.5)	51.0 (48.6-53.4)	34.3 (32.0-36.5)	14.0 (12.3-15.7)	63.4 (61.1-65.8)
2 nd degree	686 (20.6)	53.9 (50.1-57.6)	36.3 (32.7-39.9)	16.4 (13.6-19.2)	66.6 (62.9-70.2)
1 st degree	417 (12.5)	47.5 (42.7-52.4)	24.0 (19.9-28.2)	11.4 (8.3-14.5)	57.3 (52.4-62.2)
1 st & 2 nd degree	332 (10.0)	47.5 (42.1-53.0)	30.7 (25.7-35.7)	10.9 (7.5-14.4)	57.2 (51.7-62.7)
Unknown ⁷	178 (5.4)	54.5 (47.2-61.8)	29.8 (23.0-36.5)	9.7 (5.3-14.1)	64.0 (56.9-71.1)
Individual SES					
Education					
< High school	989 (29.7)	47.7 (44.5-50.8)	29.7 (26.8-32.6)	12.9 (10.8-15.1)	60.2 (57.0-63.3)
High school/certificate	1,102 (33.1)	51.9 (48.9-54.8)	34.9 (32.1-37.7)	14.9 (12.8-17.0)	64.3 (61.4-67.2)
≥Diploma	1,235 (37.1)	52.8 (50.0-55.6)	33.4 (30.7-36.0)	13.1 (11.2-15.0)	63.3 (60.5-66.0)
Employment					
Unemployed/retired	1,367 (41.1)	46.9 (44.2-49.6)	28.5 (26.1-30.9)	12.5 (10.7-14.2)	57.7 (55.1-60.4)
Employed ⁹	1,941 (58.4)	53.9 (51.7-56.2)	35.9 (33.8-38.1)	14.6 (13.0-16.2)	66.3 (64.2-68.5)
Unknown ⁷	18 (0.5)	44.4 (20.8-68.1)	22.2 (2.5-42.0)	0.0 (-)	50.0 (26.2-73.8)
Income					
<\$52,000	1,216 (36.6)	49.1 (46.2-51.9)	30.0 (27.4-32.6)	12.3 (10.4-14.2)	60.4 (57.5-63.2)
\$52,000-\$129,999	1,271 (38.2)	52.1 (49.3-54.9)	35.9 (33.2-38.5)	15.6 (13.6-17.6)	65.2 (62.5-67.9)
≥\$130,000	476 (14.3)	54.9 (50.4-59.4)	36.0 (31.7-40.4)	12.9 (9.8-16.0)	65.9 (61.5-70.2)
Unknown ⁷	363 (10.9)	48.5 (43.2-53.7)	27.1 (22.5-31.7)	12.0 (8.6-15.5)	57.7 (52.5-63.0)
Number of cars					
None	132 (4.0)	53.9 (45.2-62.6)	29.2 (21.4-37.1)	9.9 (4.8-15.1)	65.6 (57.4-73.9)
1 car	1,109 (33.3)	50.6 (47.6-53.6)	30.9 (28.2-33.7)	13.6 (11.6-15.6)	62.6 (59.7-65.5)
2 cars	1,407 (42.3)	51.0 (48.4-53.7)	32.8 (30.3-35.2)	13.8 (12.0-15.7)	62.6 (60.0-65.2)
>2 cars	601 (18.1)	52.8 (48.8-56.8)	37.5 (33.6-41.4)	14.1 (11.2-16.9)	64.1 (60.2-68.1)
Unknown ⁷	77 (2.3)	36.8 (25.9-47.8)	29.3 (19.0-39.7)	13.5 (5.7-21.4)	51.4 (39.8-63.0)
Marital status¹⁰					
Married	2,440 (73.4)	50.7 (48.7-52.7)	33.7 (31.8-35.6)	14.4 (13.0-15.8)	62.8 (60.8-64.7)
Not married	886 (26.6)	51.9 (48.5-55.2)	30.2 (27.1-33.2)	11.4 (9.3-13.6)	62.6 (59.3-65.8)
Language speaks at home					
English	3,149 (94.7)	50.9 (49.1-52.7)	32.8 (31.2-34.5)	13.7 (12.5-14.9)	62.6 (60.8-64.3)
Other	177 (5.3)	52.9 (45.4-60.3)	32.2 (25.2-39.1)	12.8 (7.8-17.8)	65.5 (58.3-72.7)
Private insurance					
Full insurance	2,110 (63.4)	47.8 (45.6-49.9)	32.8 (30.8-34.8)	13.7 (12.2-15.2)	60.8 (58.6-62.9)
No/part insurance	1,215 (36.5)	56.7 (53.9-59.5)	32.9 (30.2-35.5)	13.5 (11.5-15.4)	66.2 (63.5-69.0)
Unknown ⁷	1 (0.0)	0.00 (-)	0.00 (-)	0.0 (-)	0.0 (-)
Area-level factors					
Remoteness					
Major city	1,969 (59.2)	49.8 (47.6-52.0)	31.5 (29.5-33.6)	12.7 (11.2-14.2)	61.3 (59.1-63.5)
Inner regional	804 (24.2)	53.8 (50.3-57.2)	35.6 (32.3-38.9)	14.9 (12.4-17.4)	65.7 (62.3-69.0)
Outer regional/remote	553 (16.6)	51.1 (46.9-55.3)	33.2 (29.3-37.2)	15.0 (12.0-18.1)	63.5 (59.4-67.7)
Accessibility to treatment					
High accessibility	2616 (78.7)	50.5 (48.6-52.5)	32.4 (30.6-34.2)	13.2 (11.9-14.5)	62.0 (60.1-63.9)
Low accessibility	710 (21.4)	52.6 (48.9-56.3)	34.3 (30.8-37.8)	15.3 (12.7-18.0)	65.4 (61.8-68.9)
Area disadvantages					
Least disadvantaged	737 (22.2)	47.7 (44.1-51.4)	31.8 (28.4-35.2)	12.5 (10.1-14.9)	58.6 (55.0-62.3)
Middle SES	2,014 (60.6)	51.2 (49.0-53.4)	32.8 (30.7-34.9)	13.8 (12.3-15.4)	63.4 (61.2-65.5)
Most disadvantaged	575 (17.3)	54.5 (50.4-58.6)	34.0 (30.1-37.9)	14.5 (11.6-17.4)	65.6 (61.7-69.6)

1. 95% confidence intervals (CI) were calculated as mean±1.96se; 2. Participants with missing values in stage (n=59) were excluded from the calculation; 3. Participants with missing values in grade (n=45) were excluded from the calculation; 4. Participants with missing values in hormone receptors status (n=106) were excluded from the calculation; 5. High severity was defined as either Stage II-IV, or Grade 3, or HR-. Participants with missing values in overall severity (n=167) were excluded from the calculation; 6. BMI: body mass index. Overweight defined as BMI≥25; 7. Unknown values were treated as missing data for the final data analysis and were handled with multiple imputation. 8. HRT: hormone replacement therapy; 9. Including full-time and part-time employment; 10. Married include those living as married, unmarried include those not living as married.

Table 2 Odds ratios of breast cancer diagnosed with late stage, high grade, or negative hormone receptors by different factors.

	Stage II-IV		Grade 3		HR-	
	Adjusted OR ¹ (95% CI)	p-value	Adjusted OR ² (95% CI)	p-value	Adjusted OR ³ (95% CI)	p-value
Method of detection		<0.01		<0.01		<0.01
Screening	1		1		1	
Symptoms	3.63 (3.09-4.27)	<0.01	2.25 (1.91-2.66)	<0.01	2.42 (1.92-3.05)	<0.01
Frequency of screening		<0.01		0.12		0.19
At least two-yearly	1		1		1	
Infrequently	1.74 (1.39-2.18)	<0.01	1.24 (1.00-1.55)	0.05	0.93 (0.70-1.24)	0.62
None	1.89 (1.48-2.42)	<0.01	1.15 (0.91-1.45)	0.25	0.74 (0.54-1.03)	0.07
Age of diagnosis		<0.01		<0.01		0.69
70-79	1		1		1	
60-69	1.04 (0.82-1.33)	0.75	1.06 (0.81-1.38)	0.67	1.12 (0.78-1.60)	0.54
50-59	1.43 (1.11-1.84)	0.01	1.31 (1.00-1.71)	0.05	1.19 (0.82-1.74)	0.36
<50	1.62 (1.21-2.17)	<0.01	1.62 (1.19-2.22)	<0.01	1.02 (0.68-1.54)	0.92
Lifestyle						
BMI⁴		<0.01		0.14		
Healthy weight	1		1		-	
Overweight	1.43 (1.22-1.67)	<0.01	1.13 (0.96-1.32)	0.14	-	
Smoking		0.01		0.04		0.01
Current smoker	1		1		1	
Used to smoke	1.27 (0.94-1.71)	0.11	1.23 (0.91-1.66)	0.18	1.14 (0.74-1.74)	0.55
Never smoked	1.40 (1.05-1.87)	0.01	1.41 (1.05-1.88)	0.02	1.53 (1.02-2.31)	0.04
Reproductive history						
Duration of menstruation				<0.01		0.03
>35 years	-	-	1		1	
≤35 years	-	-	1.34 (1.13-1.59)	<0.01	1.29 (1.03-1.62)	0.03
Menopause		<0.01		<0.01		
No	1		1		-	-
Yes	1.98 (1.57-2.50)	<0.01	1.41 (1.13-1.78)	<0.01	-	-
Age started using contraceptives						0.12
Never used	-	-	-	-	1	
≤18	-	-	-	-	1.42 (0.96-2.10)	0.08
>18	-	-	-	-	1.13 (0.80-1.59)	0.50
Duration of contraceptives using				0.03		
Never or <2 years	-	-	1		-	-
2-10 years	-	-	1.29 (1.04-1.60)	0.02	-	-
>10 years	-	-	1.33 (1.07-1.67)	0.01	-	-
Family history						
Relatives with breast or ovarian cancer				0.01		
1 st degree	-	-	1		-	-
1 st & 2 nd degree	-	-	1.30 (0.93-1.83)	0.12	-	-
2 nd degree	-	-	1.54 (1.16-2.05)	<0.01	-	-
None	-	-	1.49 (1.15-1.92)	<0.01	-	-
Individual SES						
Private insurance		<0.01				
Full insurance	1		-	-	-	-
No/part insurance	1.32 (1.12-1.54)	<0.01	-	-	-	-
Area-level factors						
Remoteness				0.04		
Major city	-	-	1		-	-
Inner regional	-	-	1.26 (1.05-1.52)	0.01	-	-
Outer regional/Remote	-	-	1.12 (0.91-1.38)	0.30	-	-
Accessibility to treatment						0.12
High accessibility	-	-	-	-	1	
Low accessibility	-	-	-	-	1.21 (0.95-1.55)	0.12

1. Odds ratios were generated using Model 1; 2. Odds ratios were generated using Model 2; 3. Odds ratios were generated using Model 3; 4. BMI: body mass index. Overweight defined as BMI ≥ 25.

Table 3 Crude percentages and adjusted odds ratios of diagnosed with high severity breast cancer stratified by women detected by screening or symptoms

	By screening			By Symptoms		
	Crude percentage ¹	Adjusted OR ² (95% CI)	p-value	Crude percentage	Adjusted OR ³ (95% CI)	p-value
Frequency of screening			0.05			<0.01
At least two-yearly	46.1	1		72.8	1	
Infrequently	55.8	1.45 (1.01-2.07)	0.04	85.0	2.07 (1.47-2.90)	<0.01
None	56.1	1.46 (0.91-2.34)	0.12	83.2	1.95 (1.39-2.74)	<0.01
Age of diagnosis			0.15			0.11
70-79	43.9	1		74.2	1	
60-69	45.0	0.96 (0.71-1.30)	0.79	75.1	1.15 (0.75-1.76)	0.52
50-59	50.6	1.15 (0.81-1.64)	0.43	79.5	1.65 (1.02-2.69)	0.04
<50	51.5	1.47 (0.94-2.29)	0.09	80.3	1.73 (1.00-2.99)	0.05
Lifestyle						
BMI⁴			0.10			<0.01
Healthy weight	44.1	1		73.1	1	
Overweight	49.1	1.20 (0.97-1.49)	0.10	82.2	1.67 (1.31-2.14)	<0.01
Smoking			0.02			
Current smoker	38.0	1		-	-	-
Used to smoke	46.7	1.52 (0.99-2.36)	0.06	-	-	-
Never smoked	49.0	1.77 (1.16-2.71)	0.01	-	-	-
Reproductive history						
Menopause			<0.01			<0.01
No	39.7	1		74.2	1	
Yes	48.6	2.01 (1.42-2.84)	<0.01	79.5	2.01 (1.43-2.82)	<0.01
Duration of HRT⁵						0.04
>10 years	-	-	-	67.5	1	
2-10 years	-	-	-	71.1	1.10 (0.66-1.82)	0.72
Never or <2 years	-	-	-	80.1	1.60 (1.02-2.51)	0.04
Individual SES						
Education						0.15
<High school	-	-		74.9	1	
High school/certificate	-	-		80.3	1.35 (0.98-1.85)	0.07
≥Diploma	-	-		78.6	1.29 (0.94-1.76)	0.12
Employment			<0.01			0.08
Unemployed/retired	42.5	1		78.4	1	
Employed	52.1	1.46 (1.15-1.85)	<0.01	78.2	0.75 (0.54-1.03)	0.08
Private insurance			0.08			
Full insurance	46.1	1		-	-	-
No/part insurance	50.2	1.22 (0.98-1.51)	0.08	-	-	-
Area-level factors						
Remoteness			0.17			
Major city	45.5	1		-	-	-
Inner regional	50.9	1.26 (0.99-1.60)	0.07	-	-	-
Outer regional/remote	49.3	1.13 (0.86-1.49)	0.37	-	-	-

1. Crude percentages were calculated from the observed data and did not adjusted for other variables. Participants with missing values in overall severity (n=167) were excluded from the calculation; 2. Odds ratios were generated using Model 5; 3. Odds ratios were generated using Model 6; 4. BMI: body mass index. Overweight defined as BMI $\geq$ 25; 5. HRT: hormone replacement therapy.

Figure 1 Odds ratios of high severity breast cancer at diagnosis by detection methods.

Supplementary Table 1 Adjusted odds ratios of diagnosed with high severity breast cancer stratified by screening facilities among women detected by screening

	Screened in Public Facilities		Screened in Private Facilities	
	Adjusted OR ¹ (95% CI)	p-value	Adjusted OR ² (95% CI)	p-value
Frequency of screening		0.10		0.43
At least two-yearly	1		1	
Infrequently	1.41 (0.95-2.11)	0.09	1.74 (0.74-4.08)	0.21
None	1.46 (0.91-2.34)	0.13	1.21 (0.51-2.86)	0.67
Age of diagnosis		0.02		0.74
70-79	1		1	
60-69	0.89 (0.63-1.26)	0.53	1.14 (0.57-2.27)	0.71
50-59	1.24 (0.83-1.85)	0.29	0.84 (0.38-1.82)	0.65
<50	1.74 (1.03-2.92)	0.04	0.93 (0.37-2.36)	0.88
Lifestyle				
BMI³		<0.01		0.14
Healthy weight	1		1	
Overweight	1.46 (1.13-1.88)	<0.01	0.72 (0.46-1.11)	0.14
Smoking		0.16		0.13
Current smoker	1		1	
Used to smoke	1.42 (0.87-2.30)	0.16	1.66 (0.55-4.98)	0.37
Never smoked	1.56 (0.98-2.50)	0.06	2.35 (0.80-6.86)	0.12
Reproductive history				
Menopause		<0.01		<0.01
No	1		1	
Yes	1.81 (1.21-2.73)	<0.01	2.81 (1.41-5.60)	<0.01
Individual SES				
Employment		0.07		<0.01
Unemployed/retired	1		1	
Employed	1.29 (0.98-1.70)	0.07	2.24 (1.37-3.66)	<0.01
Private insurance		0.50		0.01
Full insurance	1		1	
No/part insurance	1.09 (0.85-1.38)	0.50	2.10 (1.18-3.73)	0.01
Area-level factors				
Remoteness		0.41		0.11
Major city	1		1	
Inner regional	1.16 (0.88-1.53)	0.29	1.66 (0.96-2.88)	0.07
Outer regional/remote	1.18 (0.88-1.59)	0.27	0.72 (0.31-1.71)	0.46

1. Odds ratios were generated using Model 7, Model 7 used the same variables included in Model 5; 2. Odds ratios were generated using Model 8, Model 8 used the same variables included in Model 5; 3. BMI: body mass index. Overweight defined as BMI $\geq$ 25.

Supplementary Figure 1 Time interval between diagnosis and the returning of self-administered questionnaire.

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