Multilevel determinants of breast cancer survival: association with geographic remoteness and area-level socioeconomic disadvantage.

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ABSTRACT

A major priority for cancer control agencies is to reduce geographical inequalities in cancer outcomes. While the poorer breast cancer survival among socioeconomically disadvantaged women is well established, few studies have looked at the independent contribution that area- and individual-level factors make to breast cancer survival. Here we examine relationships between geographic remoteness, area-level socioeconomic disadvantage and breast cancer survival after adjustment for patients' socio- demographic characteristics and stage at diagnosis.

Multilevel logistic regression and Markov chain Monte Carlo simulation were used to analyze 18 568 breast cancer cases extracted from the Queensland Cancer Registry for women aged 30 to 70 years diagnosed between 1997 and 2006 from 478 Statistical Local Areas in Queensland, Australia.

Independent of individual-level factors, area-level disadvantage was associated with breast-cancer survival (p=0.032). Compared to women in the least disadvantaged quintile (Quintile 5), women diagnosed while resident in one of the remaining four quintiles had significantly worse survival (OR 1.23, 1.27, 1.30, 1.37 for Quintiles 4, 3, 2 and 1 respectively).) Geographic remoteness was not related to lower survival after multivariable adjustment. There was no evidence that the impact of area-level disadvantage varied by geographic remoteness. At the individual level, Indigenous status, blue collar occupations and advanced disease were important predictors of poorer survival.

A woman's survival after a diagnosis of breast cancer depends on the socio-economic characteristics of the area where she lives, independently of her individual-level characteristics. It is crucial that the underlying reasons for these inequalities be identified to appropriately target policies, resources and effective intervention strategies.

INTRODUCTION

Worldwide, breast cancer (BC) is the most commonly diagnosed cancer among women, accounting for 23% of total cancer cases in 2008, and is the leading cause of cancer death among women (14% of cancer deaths in 2008).[1] Global incidence and mortality rates vary by more than five-fold with developed countries often having high incidence but relatively low mortality rates.[1]

Consistent with other developed countries, [1] BC survival in Australia has improved significantly over the last few decades,[2,3] most likely due to earlier detection through mammographic screening and advances in both primary and adjuvant BC treatments.[4]

Despite having one of the highest female BC survival rates in the world,[5] there is significant geographical variation in survival in Australia, with poorer prognosis for women diagnosed outside urban areas and for those living in socioeconomically disadvantaged regions[6,7,3] even after controlling for stage at diagnosis.[8,7] International studies have consistently shown worse survival in women with lower levels of education or income, [9] and an inverse association between area-disadvantage and BC survival.[10-12] Emerging evidence however suggests a temporal narrowing of such disparities in some developed countries.[13]

Due to the potential barriers of distance and access to specialized care, it could be expected that women living in more rural and remote areas would have poorer survival. However results have been inconclusive. While studies from Australia report poorer BC survival in rural areas,[6,14] a New Zealand study found no geographical differences[15] while a Canadian study found lower survival with increasing urbanization.[16]

Most studies of area-disadvantage and remoteness inequalities in BC survival have used ecological measures of neighborhood disadvantage.[10,11,6,12,7] Hence they cannot indicate whether, and to what extent, geographical differences are due to individual or area-level effects. Multilevel survival models allow for the partitioning and modeling of complex sources of area- and individual-level variation and thus enable us to determine whether areas have an impact on breast cancer survival

independently of the characteristics of women who live in those areas. When analyzing hierarchical event data, these survival models should be used to account for clustering of individuals within the same geographical location.[17,18] Until recently however computational requirements have limited their use especially for large health-related data sets having long follow up periods and relatively rare events.[19,9]

To date, no known Australian study has used multilevel analysis to describe the relationship between BC survival, geographic remoteness, area disadvantage and individual-level socioeconomic status (SES). Additionally, there has been only minimal research on whether individual clinical and demographic characteristics mediate survival disparities between social groups.[20] This current study considers the impact of geographic remoteness and area disadvantage on BC survival among Queensland women after adjusting for stage at diagnosis and other individual-level variables. Specifically, we aimed to:

(i) assess whether BC survival varied with a woman's area of residence while accounting for within-area variation in individual effects and between-group variation in area-based factors
(ii) identify individual-level factors influencing BC survival
(iii) explore the impact of area disadvantage and remoteness on survival after controlling for patient characteristics, and
(iv) investigate the effect of interactions between area-level factors on survival.

MATERIALS AND METHODS

Ethical approval to conduct this study was obtained from the University of Queensland Social and Behavioral Sciences Ethical Review Committee.

With appropriate legislative approvals incident cases were extracted from the Queensland Cancer Registry (QCR), a state-wide population-based registry to which all confirmed invasive cancers diagnosed among Queensland residents must be notified by law. All women aged 30-79 years diagnosed with invasive breast cancer (ICD-10: C50) in Queensland between January 1, 1997 and December 31, 2006 (inclusive) (n=19 544) were eligible for the study. In situ BC, tumors of unknown

size or with unknown lymph node involvement (if size < 20mm) were excluded. The study population was limited to females with first primary diagnosis of invasive BC.

Survival data

Survival information for the study cohort was examined up to 31st December 2007, providing at least one year of follow-up for each woman. Survival was measured in years from date of BC diagnosis to date of death or study end point. Since the outcome of interest was survival from breast-cancer, deaths from other causes were censored.

Disease spread: A proxy measure of BC stage was used as described previously[21]based on routinely available data on tumor diameter and lymph node involvement. Tumors of less than 20 mm diameter with no record of lymph node involvement or metastases were classified as localized BC; although absence of metastasis could not be confirmed from QCR data. Since it was not possible to definitively distinguish between Stages II to IV with the available information, these were collectively defined as 'Advanced BC' with cancers known to be diagnosed as a result of metastatic disease being included in this category.[21]

Information was obtained from QCR on year and age of diagnosis, marital status, occupation and Indigenous status, with the latter being well recorded in the Registry despite some under identification[21] (see Table 1 for categories).

Area-level variables:

Statistical Local Areas (SLAs) were used as the geographical unit for the area–level analysis (Figure 1). SLAs are typically based on or aggregate together to form local government areas, for which the local governments are responsible for service provision and infrastructure. There were 478 SLAs in Queensland in 2006, with location information being used to allocate address information in preceding years to the 2006 SLA boundaries, thus removing any impact of temporal changes in geographic boundaries.

Geographic Remoteness: Remoteness of residence when diagnosed with BC was defined using the ARIA+ classification,[22] This purely geographic measure of remoteness is determined by the minimum road distance from population localities to different levels of service centres (see Table 1 for categories).

Area disadvantage: This was measured using the Index of Relative Socioeconomic Disadvantage (IRSD),[23] which is an area-based measure of SES and considers factors such as the percentage of residents in each SLA on a low income, in unskilled occupations, and unemployed (among others). The IRSD score was assigned according to the census closest to the diagnosis date and then collapsed into five quintiles of increasing advantage (Quintile 1 most disadvantaged).

Statistical Analysis

We have utilized a full multilevel regression model for this study. This approach is substantially different to adjusting for clustering effects through random effects as described in other studies[24,25] and sometimes inappropriately referred to as multilevel modeling (synonymous with hierarchical regression). Adjusting for clustering entails adjusting the standard errors of estimates for the non-independence of data caused by individuals living within neighborhoods[26]. It is a more limited approach than multilevel modeling, in which clustering is used in informative ways[26] and which allows for the partitioning and modeling of complex sources of area- and individual-level variation.

Since the Cox proportional hazards model does not allow for full multilevel modeling, we used a discrete-time approach and an expanded person-period dataset, in which a sequence of binary responses is generated for each person from each event time, which for this analysis was years[27]. For example, if a woman dies during the third year after diagnosis then her discrete responses will be = (0,0,1), while another women who is censored in the third year will have the response vector as (0,0,0).The discrete-time hazard, h, for interval t and person i is the probability of an event during interval t, given that no event has occurred in a previous interval, i.e. $h_{ti}=Pr(y_{ti} = 1 \mid y_{si}=0, s<t)$. This is the usual response probability for a binary variable.

Multilevel logistic regression was used to analyze the expanded person-period data set to assess whether geographic remoteness and area disadvantage were associated with BC survival after adjustment for individual effects. Models were fitted using Markov chain Monte Carlo (MCMC) techniques in MLwiN version 2.15 (University of Bristol, United Kingdom)[28] and checked for convergence with Raftery-Lewis and Brooks-Draper diagnostic tools. We used 40,000 iterations for burn in and 80,000 iterations for parameter estimation. A second-order polynomial (ie. time (years) and time-squared) was used to describe the underlying hazard[17]. The Bayesian deviance information criterion (DIC),[29] was used to assess model fit with smaller values indicating better fit.

A three-step analytical approach was used. First, we specified a null model that comprised individuals (level 1) nested in SLAs (level 2) without any explanatory factors. A significant SLA-level random term (indicated using Wald chi-square)[30] suggests between-SLA variation in BC survival. Second patient characteristics (Model 2), and then area-level geographic remoteness (Model 3) or neighborhood disadvantage (Model 4) were added. The final model (Model 5) included all explanatory variables on all levels simultaneously. These models allowed us to estimate the independent contribution of patient- and area -level factors on survival. Interactions between area-level remoteness and disadvantage were tested (Wald chi-square) by including all second-order terms and main effects of these variables in the fully adjusted model. Parameter estimates are presented as odds ratios (OR) with their 95% confidence intervals (CI) similar to that reported by other multilevel studies[31,18]carried out using non informative priors where Bayesian and maximum likelihood estimates are likely to be close.[32] Joint chi-square tests were used to assess the contribution of each variable to model fit and the Z test to assess the significance of individual coefficients.

RESULTS

Study population

Selected characteristics of the study population are summarized in Table 1. During the study period almost half (47%) of 18 568 participants were diagnosed with advanced disease and 1514 women

(8%) died due to BC. The mean length of follow-up was 4.3 years (median=4 years, range=0-10 years). The overall five-year BC survival rate for study participants was 90% (95% CI=90-91%).

Random effects

In the multivariable logistic regression analyses (Table 2), the null model (Model 1) showed there was significant (p=0.041) variation in BC survival across the SLAs. This area-level variation was successively reduced and became non-significant with multivariable adjustment for the remaining individual- and area-level effects. About 70% of the total between-SLA variation was explained by patient-level factors fitted in Model 2.

The DIC statistic showed that adding in the individual effects (Model 2) gave significantly improved fit compared to the null model (Model 1). Compared to Model 2, adding in area disadvantage (Model 4) further reduced the DIC by around 5 units; whereas there was no evidence for better fit by adding in area-level remoteness. The DIC were similar for Models 2 and 3 and increased for fully adjusted Model 5, hence Model 4 was the best fitting model for these data. Regardless of the final model chosen, point estimates for the individual-level covariates did not vary markedly across the different models.

Fixed effects

Geographic remoteness: Since the final model (Model 4) did not include remoteness, there was no statistically significant evidence that geographical remoteness was associated with breast cancer survival, after adjusting for the other individual- and area-level variables.

Area-disadvantage: Independent of individual-level factors, area disadvantage was significantly associated with breast-cancer specific survival (p = 0.032) in this final model (Model 4). Compared to women in the least disadvantaged quintile (Quintile 5), women diagnosed while resident in one of the remaining four quintiles had significantly worse survival (OR 1.23, 1.27, 1.30, 1.37 for Quintiles 4, 3, 2 and 1 respectively).

Individual-level factors: At the individual-level, cancer stage, age at diagnosis and Indigenous status were significantly associated ($p< 0.001$) with survival (Model 4, Table 2). Poorer survival across all areas of Queensland (irrespective of area-level variables) were seen for patients aged between 30 to34 or older than 70 compared to those aged 50-54; blue collar workers versus professionals, Indigenous women versus non-Indigenous and unmarried (divorced or separated) versus married women. Women diagnosed with advanced BC (OR: 4.94, CI: 4.34-5.66, $p< 0.001$) had a significant survival disadvantage relative to those diagnosed with localized tumors. Also BC survival was lowest in the first three years after diagnosis and then increased, with a significant quadratic relationship between survival and years of follow-up.

Interaction effects

Analyses stratified by remoteness or area disadvantage revealed no evidence of geographic variation in survival by deprivation categories or that the deprivation effect varied by remoteness status (data not shown). Interactions between geographic remoteness and disadvantage were also analysed but found not to reach statistical significance at $p \leq 0.10$ using Wald Chi-square test (results not shown). Overall fit of the interaction model was poorer (DIC higher by > 12 units) than its main-effects counterpart which suggests that the association between deprivation and poorer BC survival was similar for women from major cities as for those from rural or remote areas.

DISCUSSION

Using a large population cohort of Queensland women diagnosed with breast cancer, we found that the characteristics of the area in which a woman lives, specifically area disadvantage, was related to BC survival independently of individual prognostic factors including diagnosis stage.

While we found significant evidence of a bivariate association between remoteness and BC survival, there was no association after adjusting for stage at diagnosis and other individual-level variables. Consistent with this we have recently demonstrated that women from remote or rural regions of Queensland are more likely to present with late-stage BC,[21] and so this result highlights the importance of improving early diagnosis of BC to reduce the existing geographical differences in BC survival.[33,8]

In contrast, the significant bivariate variation in BC survival by area disadvantage remained after adjusting for stage at diagnosis. Our previous analysis [21] demonstrated that BC was more likely to be diagnosed at an advanced stage among women living in disadvantaged areas; hence these women had less favorable survival outcomes. However our current results reveal there is an additional survival inequality over and above that caused by stage at diagnosis. This is consistent with widely reported gap in BC survival across socio-economic categories found in Australia,[8,7] Netherlands,[10,11] USA[9,12] and UK[34] that was moderated but still remained significant after controlling for various demographic and prognostic factors

Lower BC survival in more disadvantaged areas is increasingly thought to reflect the combined effect of multiple factors [10,11,14,35,6,3,12,7] such as educational, economic and socio- cultural factors that affect access to early diagnostic and treatment services as well as environmental or lifestyle factors that affect health behavior and disease risk. Routine mammographic screening detects smaller low-grade invasive tumors before women become symptomatic, improves therapeutic effectiveness [36] and has led to survival benefits among women aged 50-69 years,[37] with significantly improved survival for screen-detected tumors.[38] Internationally, relatively disadvantaged women are less likely to be screened for BC.[10,9] Although Australian women living in affluent areas have lower

participation rates in the national publicly-funded BreastScreen Australia screening program,[37] the extent of private screening among this group is unknown. It is also unlikely that access issues related to distance [35,39] would entirely explain this effect, since, based on Model 5, the socioeconomic gradient in our study persisted after adjusting for area-level remoteness. Some studies have related the survival gap to treatment differences across social groups and lower adherence to therapeutic guidelines with increasing deprivation.[11,35,12] Deprivation has also been associated with a higher prevalence of more aggressive tumors with poorer prognosis.[40] Data on the expression of BC tumor biomarkers were not available for our cohort and could not be included in this analysis.

Age-related patterns of BC survival in our study are consistent with other reports.[3,41] The survival disadvantage for older women (> 75 years) may reflect age-related treatment variations and sub-optimal clinical management.[34,42] Although relatively rare, breast cancers diagnosed in women younger than 35 years are more likely to be detected later [36] when symptomatic [21,41] and to be more aggressive, less responsive and with a poorer prognosis.[41]

While we were limited in our ability to investigate temporal changes in survival, two-year survival estimates increased over the three time periods. This is consistent with decreasing Australian [8] and international[1] BC mortality rates over time, with these changes generally attributed to earlier detection through mass screening and advances in BC treatments.[4] However screening rates were relatively stable over the study period[8] suggesting that better management of invasive BC through establishment of clinical protocols[43] and expanded treatment options[44] especially hormonal, systemic and targeted therapies may have played a greater role.

Given their relatively small numbers (1%) in the study cohort, the persistent survival deficit for Indigenous women even after controlling for geographic location, stage, patient- and area disadvantage highlights both the strength of this effect and the complexity of underlying reasons. Indigenous women in Queensland also have lower screening rates than the general population[8] and higher risks of advanced BC.[21] These effects are consistent with results of previous national and state/territory studies in Australia.[45,46] Probable reasons include a lack of knowledge of symptoms

and treatment among Indigenous women, longer diagnostic delays, limited access to and uptake of optimal care, corresponding poorer quality of care, more co-morbidities as well as cultural beliefs that may act as barriers to health care utilization.[46,45]

Strengths of this study include having a cohort consisting of all Queensland female breast cancer patients diagnosed from 1997 to 2006 with information on stage at diagnosis. All study data were collected prospectively for administrative purposes independently of the study hypotheses, thus eliminating recall bias. Our methodology specifically allows for the simultaneous estimation of the effects of individual- and area-level effects, quantifies area-level variation in survival, and reports on both the magnitude and significance of all included explanatory variables.

Several study limitations should be noted. Investigation of other possible confounders influencing BC survival such as screening history,[10,9] comorbidities,[10] tumor biology,[40]health insurance, [47] treatment [47,39,12] or lifestyle [9] was not possible as these data are not collected as part of the QCR. Also the individual-level SES variables were restricted to occupation; hence we could not control for within-area variations in other relevant sources of socioeconomic inequalities such as education and income that may impact outcomes through different mechanisms. [9] This leaves open the possibility of residual confounding by unmeasured socioeconomic indicators although our multi-level strategy allows appropriate adjustment for patient- and area-level disadvantage by contrast to ecological designs. Study results could also have been influenced by the lack of sensitivity and specificity of our measure of occupation since the "Not stated" group could not be disaggregated into more homogenous groups. Cancer-specific estimates were used for the analyses hence inaccuracies in cause of death coding may bias results and underestimate actual BC mortality.[48]

Conclusion

This study illustrates the significant association between area disadvantage and BC survival, independent of stage at diagnosis and other individual-level characteristics. Further study is required to disentangle the role of clinical, educational, cultural, demographic and other factors, particularly those contributing to socioeconomic differences for Indigenous and disadvantaged women. Achieving

equitable cancer care through targeted strategic planning, is a major priority for cancer control agencies.[49] Greater understanding of the causes underlying socio-demographic and spatial patterns of cancer indicators is important for targeting policies, resources and effective intervention strategies to minimize inequalities in BC stage and outcomes.[50]

Figure 1: Geographical boundaries of the Statistical Local Areas in Queensland based on the 2006 Australian Standard Geographical Classification.

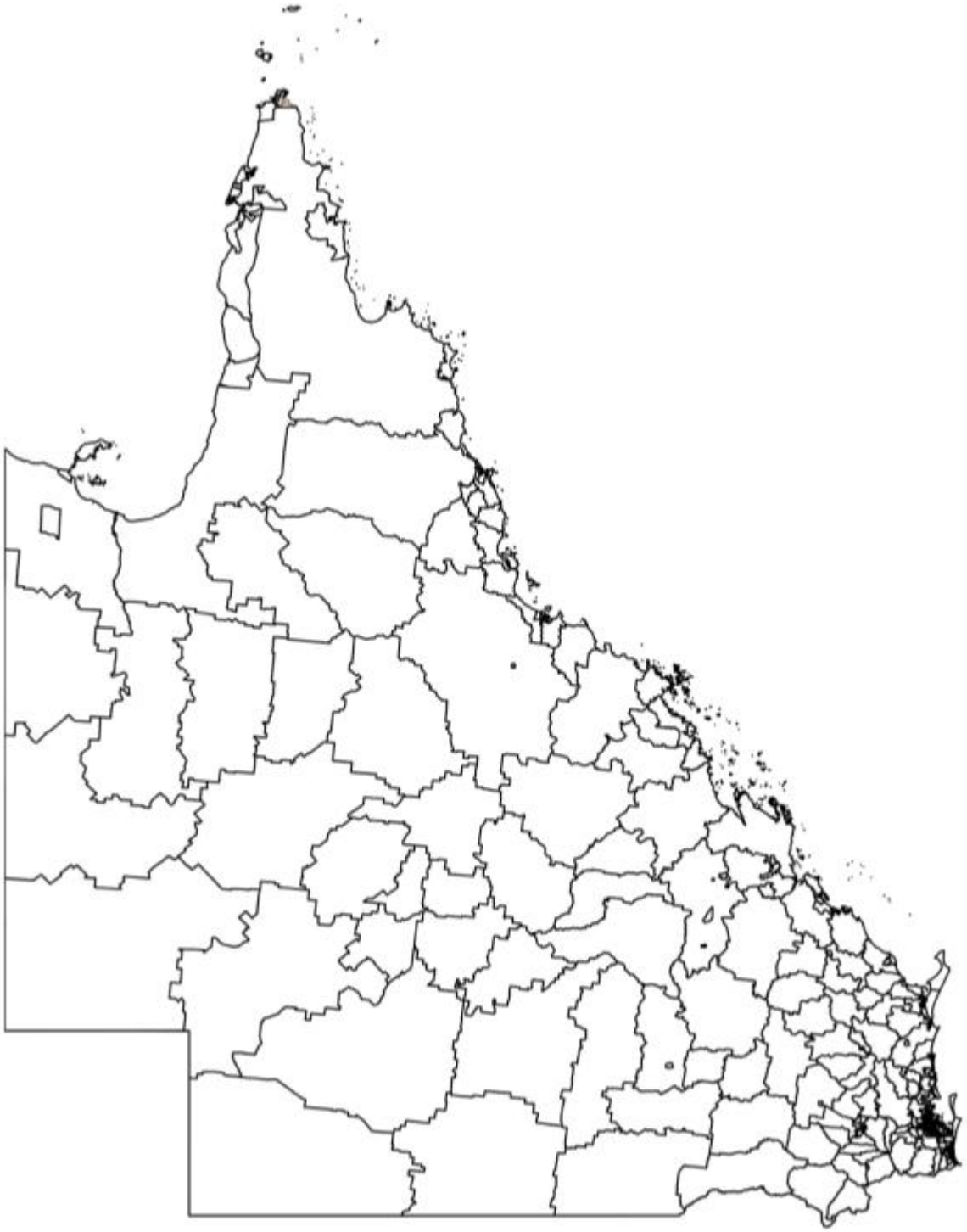

Table 1: Cohort description and survival outcomes for females diagnosed with breast cancer during the period 1997-2006

	All breast cancer (N)	Breast cancer deaths (%)	2 yr survival (%)	5 yr survival (%)
All women in cohort	18 568	8.2	96.4 [96, 97]	90.3 [90,91]
Area-level variables				
Area-Remoteness Index of Australia (ARIA)		X^2=9.84, df=3, p=0.022		
Major city	11 255	7.8	96.6 [96, 97]	91.2 [90, 92]
Inner regional	4037	8.6	96.4 [95, 97]	89.4 [88, 91]
Outer regional	2580	8.8	95.8 [95, 97]	88.7 [87, 91]
Remote/Very remote	696	9.2	95.0 [93, 97]	88.4 [85, 91]
Index of Relative Socioeconomic Disadvantage (IRSD)		X^2=24.75, df=4 ,p<0.001		
Q5 (least disadvantaged)	3019	6.1	97.8 [97, 98]	93.4 [92, 94]
Q4	4657	8.0	96.7 [96, 97]	90.7 [90, 92]
Q3	4540	8.4	96.2 [96, 97]	89.7 [89. 91]
Q2	4198	9.2	95.6 [95, 96]	88.7 [87, 90]
Q1 (most disadvantaged)	2151	8.9	95.8 [95, 97]	89.9 [88, 91]
Year of diagnosis		X^2=15.79, df=4, p<0.001		
1997 – 2000	6714	13.9	96.0 [95, 96]	89.4 [89, 91]
2001 – 2003	5688	8.0	96.5 [96, 97]	90.1 [90, 92]
2004 - 2006	6166	2.0	96.9 [96, 97]	missing
Individual-level variables				
Age		X^2=75.89, df=4, p<0.001		
30-34	321	15.3	93.3 [90, 96]	81.5 [76, 86]
35-39	819	11.4	95.4 [94, 97]	87.4 [84, 90]
40-44	1624	9.4	95.5 [94, 96]	88.7 [87, 91]
45-49	2407	6.6	97.5 [97, 98]	92.0 [90, 93]
50-54	2729	7.7	96.8 [96, 97]	91.3 [90, 92]
55-59	2815	6.8	97.3 [97, 99]	92.2 [91, 93]
60-64	2553	6.8	96.9 [96, 98]	91.4 [90, 93]
65-69	2132	8.3	96.7 [96, 97]	90.4 [89, 92]
70-74	1801	8.6	96.1 [95, 97]	89.9 [88, 91]
75-79	1367	11.5	93.2 [92, 94]	86.4 [84, 88]
Tumor Stage		X^2=676.57, df=1, p<0.001		
Early	9820	2.8	99.1 [98, 99]	96.9 [96, 97]
Advanced	8748	14.1	93.3 [93, 94]	82.8 [82, 84]
Indigenous status		X^2=127.10, df=2, p<0.001		
Non-Indigenous	15 705	9.4	95.9 [95, 96]	89.0 [88, 90]
Indigenous	202	14.9	91.5 [86, 95]	77.6 [69, 84]
Not stated	2661	0.5	99.8 [99, 100]	99.4 [99, 100]
Occupation		X^2=307.85, df=4, p<0.001		
Professional	3749	11.0	95.6 [95, 96]	86.8 [85, 88]
White collar	3062	12.8	94.3 [93, 95]	85.3 [84, 87]
Blue collar	715	15.9	92.9 [91, 95]	82.0 [78, 85]
Not in the labor force	7168	7.8	96.5 [96, 97]	91.3 [91, 92]
Not stated	3837	1.0	99.5 [99, 100	98.7 [98, 99]
Marital status		X^2=50.94, df=4 p<0.001		
Married	12 337	7.4	96.9 [96, 97]	91.1 [90, 92]
Never married	1067	9.1	95.2 [94, 96]	88.3 [86, 91]
Widowed	2321	11.6	95.0 [94, 96]	87.9 [86, 89]
Divorced	1702	10.6	95.0 [94, 96]	87.8 [86, 90]
Separated	568	9.3	95.2 [93, 97]	87.8 [84, 91]
Unknown	573	1.2	99.4 [98, 100]	98.2 [96, 99]

Table 2: Geographic remoteness, area-disadvantage and the odds of mortality due to breast cancer, Queensland, 1997-2006

	Model 1	Model 2		Model 3		Model 4		Model 5	
Fixed effects		**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Area-Remoteness Index of Australia									
Major city				1.00	--			1.00	--
Inner regional				1.07	0.93, 1.24			1.01	0.90, 1.12
Outer regional				1.15	1.01, 1.35			1.11	0.96, 1.25
Remote/Very Remote				1.26	0.95, 1.69			1.18	0.99, 1.53
p-value				0.060				0.366	
Index of relative socio-economic disadvantage (IRSD)									
Quintile 5 (least disadvantaged)						1.00	--	1.00	--
Quintile 4						1.23	1.08 1.56	1.25	1.06, 1.48
Quintile 3						1.27	1.06, 1.54	1.24	1.04, 1.56
Quintile 2						1.30	1.09, 1.58	1.27	1.04, 1.51
Quintile 1 (most disadvantaged)						1.37	1.11, 1.69	1.31	1.07, 1.69
p-value						0.032		0.047	
Time (years after diagnosis)		1.33	1.21, 1.46	1.31	1.22, 1.45	1.33	1.23, 1.44	1.30	1.22, 1.43
p-value		<0.001		<0.001		<0.001		<0.001	
Time-squared ([years after diagnosis]^{squared})		0.97	0.96, 0.98	0.97	0.96, 0.98	0.97	0.96, 0.97	0.97	0.96, 0.98
p-value		<0.001		<0.001		<0.001		<0.001	
Age (years)									
30-34		1.50	1.10, 2.04	1.47	1.05, 2.05	1.51	1.10, 2.03	1.52	1.12, 2.02
35-39		1.17	0.91, 1.48	1.15	0.88, 1.48	1.17	0.92, 1.48	1.22	0.96, 1.46
40-44		1.09	0.88, 1.35	1.07	0.86, 1.33	1.09	0.85, 1.33	1.13	0.95, 1.32
45-49		0.83	0.67, 1.03	0.82	0.66, 1.02	0.83	0.66, 1.03	0.84	0.74, 1.02
50-54		1	--	1	--	1	--	1	--
55-59		1.08	0.88, 1.3	1.05	0.87, 1.3	1.07	0.84, 1.33	1.12	0.93, 1.27
60-64		1.41	1.14, 1.73	1.38	1.11, 1.69	1.40	1.12, 1.67	1.43	1.23, 1.74
65-69		1.83	1.48, 2.25	1.82	1.48, 2.23	1.82	1.47, 2.25	1.90	1.57, 2.36
70-74		1.95	1.55, 2.43	1.93	1.55, 2.46	1.91	1.52, 2.36	1.99	1.59, 2.42
75-79		2.40	1.88, 3.01	2.40	1.88, 3.00	2.39	1.89, 2.96	2.40	1.99, 3.09
p-value		<0.001		<0.001		<0.001		<0.001	
I*ndigenous status*									
Non-Indigenous		1.00	--	1.00	--	1.00	--	1.00	--

	Model 1	Model 2		Model 3		Model 4		Model 5	
Fixed effects		**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Indigenous		1.72	1.17, 2.45	1.63	1.08, 2.34	1.68	1.14, 2.39	1.60	1.12, 2.1
Not stated		0.09	0.05, 0.14	0.09	0.05, 0.14	0.09	0.05, 0.15	0.09	0.05, 0.13
p-value		<0.001		<0.001		<0.001		<0.001	
Occupation									
Professional		1.00	--	1.00	--	1.00	--	1.00	--
White collar		1.05	0.91, 1.21	1.05	0.92, 1.22	1.04	0.9, 1.2	1.03	0.94, 1.15
Blue collar		1.30	1.04, 1.58	1.29	1.04, 1.57	1.26	1.02, 1.55	1.27	1.08, 1.51
Not in the labor force		0.48	0.42, 0.56	0.48	0.42, 0.55	0.47	0.41, 0.54	0.47	0.41, 0.54
Not stated		0.12	0.08, 0.16	0.12	0.08, 0.16	0.11	0.08, 0.16	0.11	0.11, 0.15
p-value		<0.001		<0.001		<0.001		<0.001	
Marital status									
Married		1.00	--	1.00	--	1.00	--	1.00	--
Never married		1.04	0.84, 1.28	1.05	0.85, 1.29	1.04	0.83, 1.27	1.04	0.88, 1.23
Widowed		1.19	1.01, 1.4	1.19	0.98, 1.38	1.18	1.01, 1.37	1.15	0.98, 1.37
Divorced		1.40	1.19, 1.65	1.42	1.22, 1.66	1.39	1.15, 1.63	1.39	1.22, 1.63
Separated		1.30	0.98, 1.7	1.30	0.99, 1.74	1.29	0.96, 1.68	1.30	1.02, 1.68
Unknown		0.84	0.35, 1.60	0.80	0.36, 1.58	0.82	0.34, 1.65	0.77	0.43, 1.85
p-value		<0.001		<0.001		<0.001		<0.001	
Cancer Stage									
early		1	--	1	--	1	--	1	--
advanced		4.96	4.37, 5.67	4.94	4.34, 5.62	4.94	4.34, 5.66	4.92	4.43, 5.62
p-value		<0.001		<0.001		<0.001		<0.001	
Random effects									
Area variance & standard error	0.027 0.018	0.008	0.015	0.013	0.015	0.006	0.009	0.009	0.013
p-value for area variance	0.041	0.389		0.154		0.318		0.391	
Percentage reduction in area variance from the null model	--	70.4		51.9		77.8		66.7	
DIC (MCMC modeling, 50, 000 iterations)	22572.34	20906.12		20905.12		20901.28		20904.07	

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