



## BAYESIAN SPATIAL ANALYSIS FOR THE EVALUATION OF BREAST CANCER DETECTION METHODS

JEFF CHING-FU HSIEH<sup>1</sup>, SUSANNA M. CRAMB<sup>2</sup>, JAMES M. MCGREE<sup>1,\*</sup>,  
PETER D. BAADE<sup>2</sup>, NATHAN A.M. DUNN<sup>3</sup> AND KERRIE L. MENGERSEN<sup>1</sup>

*Queensland University of Technology, Cancer Council Queensland and  
BreastScreen Queensland*

### Summary

This study investigated the impact of spatial location on the effectiveness of population-based breast screening in reducing breast cancer mortality compared to other detection methods among Queensland women. The analysis was based on linked population-based datasets from BreastScreen Queensland and the Queensland Cancer Registry for the period of 1997–2008 for women aged less than 90 years at diagnosis. A Bayesian hierarchical regression modelling approach was adopted and posterior estimation was performed using Markov Chain Monte Carlo techniques. This approach accommodated sparse data resulting from rare outcomes in small geographic areas, while allowing for spatial correlation and demographic influences to be included. A relative survival model was chosen to evaluate the relative excess risk for each breast cancer related factor. Several models were fitted to examine the influence of demographic information, cancer stage, geographic information and detection method on women's relative survival. Overall, the study demonstrated that including the detection method and geographic information when assessing the relative survival of breast cancer patients helped capture unexplained and spatial variability. The study also found evidence of better survival among women with breast cancer diagnosed in a screening program than those detected otherwise, as well as lower risk for those residing in a more urban or socio-economically advantaged region, even after adjusting for tumour stage, environmental factors and demographics. However, no evidence of dependency between method of detection and geographic location was found. This project provides a sophisticated approach to examining the benefit of a screening program while considering the influence of geographic factors.

**Key words:** Bayesian modelling; breast screening; Markov Chain Monte Carlo; relative excess risk; relative survival; spatial variability.

### 1. Introduction

Breast cancer is the most common invasive cancer among Australian women, accounting for an estimated 27% (or 14,560) of all cancers diagnosed among women in

\*Author to whom correspondence should be addressed.

<sup>1</sup>Queensland University of Technology (QUT), GPO Box 2434, Brisbane QLD 4001, Australia.  
e-mail: jeff.hsieh@qut.edu.au, james.mcgree@qut.edu.au, k.mengersen@qut.edu.au@qut.edu.au

<sup>2</sup>Cancer Council Queensland (CCQ), PO Box 201, Spring Hill QLD 4004, Australia.  
e-mail: sussannacramb@cancerqld.org.au; peterbaade@cancerqld.org.au

<sup>3</sup>BreastScreen Queensland (BSQ), Preventive Health Unit, Department of Health, PO Box 2368, Fortitude Valley BC QLD 4006, Australia. e-mail: nathan\_dunn@health.qld.gov.au

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2012 and is the second leading cause of cancer death in Australia (2840 deaths, or 15% of cancer deaths in 2010) (AIHW & AACR 2012). Due to the strong relationship between breast cancer stage and survival (AIHW & NBCC 2007; Baade, Turrell & Aitken 2011a), detection of breast cancer earlier in its disease pathway increases the opportunity for effective treatment to reduce the morbidity associated with this disease, and thus improve long-term prognosis. Mammography screening plays an important role in the early detection of cancer, and has been shown to improve the chance of survival (Berry *et al.* 2005, Shen *et al.* 2005).

In a climate of continuing controversy about the value of mammographic screening for reducing breast cancer mortality (McPherson *et al.* 1997; Olsen & Gtzsche 2001; Wishart *et al.* 2008), there has been strong interest in assessing the efficacy of screening programs to guide appropriate allocation of health care resources (Bordas *et al.* 2007; Hegarty, Carsin & Comber 2010; Wu *et al.* 2010). Studies over the past decade have examined the efficacy of breast cancer screening in relation to the prognosis, pathology and survival of breast cancer patients, compared against other methods of detection, and have found method of detection to be an important prognostic factor with women participating in a screening program generally having more favourable tumour stage and better survival than those detected otherwise (McPherson *et al.* 1997; Shen *et al.* 2005; Mook *et al.* 2011; Nagtegaal *et al.* 2011; Nickson *et al.* 2012).

Women whose breast cancer is diagnosed through a breast screening program tend to have better prognosis than those diagnosed symptomatically primarily because they are detected at an earlier, less advanced stage. Women with screen detected tumours are more likely to live longer and have longer time to distant recurrence than those detected otherwise (Albert *et al.* 1978; Morrison 1985; Kramer, Gohagan & Prorok 1999; Otto *et al.* 2003; Tabar *et al.* 2003; Joensuu *et al.* 2004; Shen *et al.* 2005; Bordas *et al.* 2007; Wishart *et al.* 2008; Mook *et al.* 2011). There is a suggestion that at least some of this advantage is due to lead-time and length bias, in which earlier stage tumours and those less aggressive, slow growing tumours, are more likely to be detected by screening programs (Chu, Smart & Tarone 1988; Connor, Chu & Smart 1989; Shen *et al.* 2005).

Previous studies have provided strong evidence of geographical variation in female breast cancer incidence and survival with women living in more disadvantaged or rural areas tending to have lower survival (Robshaw & Tretli 2008; Huang *et al.* 2009; Sariego 2009; Baade *et al.* 2011a; Cramb, Mengersen & Baade 2011a; Dasgupta *et al.* 2012; Cramb *et al.* 2012), even after adjusting for spread of disease at diagnosis (Dasgupta *et al.* 2012). However these analyses provide little understanding about how the impact of mammography screening on breast cancer survival varies across geographical location and by demographic sub-groups. This is of particular interest for remote Australians whose access to screening programs and treatment facilities is often limited by the barrier of distance.

A Swedish study (Bordas *et al.* 2007) investigating this topic was limited due to the homogeneous socio-economic characteristics of the study area. Studies such as these have also been constrained by the difficulty of dealing with sparse data typically associated with spatial data. Recently, Bayesian models and Markov Chain Monte Carlo (MCMC) algorithms have been used to accommodate sparse spatial data and to create disease maps to assess the spatial and possible temporal effects associated with the

disease of interest (Waller *et al.* 1997; Ghosh *et al.* 1999; Osnes & Aalen 1999; Lawson *et al.* 2000; Militino, Ugarte & Dean 2001; Lawson 2001; MacNab & Dean 2002; MacNab 2004; Richardson, Abellán & Best 2006; Hegarty *et al.* 2010; Wu *et al.* 2010; Saez *et al.* 2012).

The use of relative survival is generally preferred in survival analyses of population-based disease registry data. Relative survival compares the observed mortality among study subjects (in particular, cancer patients) to the expected mortality based on mortality in their general population counterparts. While the theory of Bayesian univariate spatial models has been extensively researched, there are few examples of Bayesian relative survival spatial models in the literature. Only Fairley *et al.* (2008), Cramb *et al.* (2011a) and Saez *et al.* (2012) have utilised additional spatial information from the neighbouring regions, thus facilitating the description of possible spatial correlation and improved estimates of relative survival cancer outcomes. To our knowledge, ours is the first study to examine the impact of geographical location on the effectiveness of breast cancer screening using a fully Bayesian spatial relative survival framework.

This study applies Bayesian spatial hierarchical relative survival models to investigate the impact of spatial location on the effectiveness of population-based breast screening in reducing breast cancer mortality, after accounting for the influence of demographics and clinical features. Specifically, this paper aims to answer the following questions:

- Q1. How do breast cancer patients' demographics, tumour stage, socio-economic status and geographic remoteness influence their relative survival?
- Q2. How do the screening programs influence the relative survival of breast cancer patients, taking into account patients' demographics, tumour stage, socio-economic status and geographic remoteness?
- Q3. Are there substantive interactions between the screening program and the patients' socio-economic status and geographic remoteness?

## 2. Methods

### 2.1. Data sources

Data were extracted from the BreastScreen Queensland (BSQ) and Queensland Cancer Registry (QCR) datasets. BreastScreen Queensland is part of the BreastScreen Australia Program which was established in 1991 by the Australian Government and the State and Territory governments. It is a public health cancer screening program that provides the only population-based breast cancer screening service in Queensland. More than 202,000 women were screened by BSQ during 2007. The Queensland Cancer Registry is a population-based registry for which notification of invasive cancers is required by law. Between 1997 and 2007, the QCR recorded over 24,000 cases of invasive breast cancer among women. Data from the QCR were linked to the BSQ data by BSQ staff using a deterministic matching process with over 90% completeness of matching. All invasive breast cancers (ICD-O-3 code = C50) diagnosed between 1 January 1997 and 31 December 2007, among Queensland women aged less than 90 years at diagnosis, were eligible for inclusion in this study. Follow-up was up to 31 December 2008.

## 2.2. Explanation of variables

The data which were analysed in the modelling process included observed mortality, age group at diagnosis (0–39, 40–49, 50–59, 60–69 and 70–89 years), marital status at time of diagnosis (married, never married, widowed/divorced/separated or unknown), indigenous status (Indigenous, non-Indigenous and unknown), tumour stage at diagnosis, detection method and geographic location and classification.

As the study includes individual-level and area-level variables, the deaths among breast cancer patients living in each Statistical Local Area (SLA) were aggregated by each individual-level variable categories. For example, the deaths among breast cancer patients living in a specific SLA, of a specific age group, with the tumour diagnosed at certain stage and method etc. were aggregated together. Statistical Local Areas were used to define geographical location. These areas are spatial units likely to be socially and economically relevant to their residents. They were specified using the 2006 version of the Australian Standard Geographical Classification. In 2006, there were 478 SLAs in Queensland with a median population of 5810.

Stage at diagnosis was classified into groups of localised, advanced and unknown using information on tumour diameter and lymph-node involvement collected by the QCR (Baade *et al.* 2011a).

Standard BSQ definitions (provided by BSQ staff) were used to categorise the method of detecting breast cancer into screen detected, interval detected and non-screen detected. Screen detected breast cancers are those diagnosed through a systematic method (e.g. mammography) during a regular BreastScreen Australia screening episode. An interval breast cancer is any invasive breast cancer diagnosed in the 24-month interval following a negative screening episode and before the next scheduled screening examination (Kavanagh *et al.* 1999). A non-screen detected breast cancer is defined as either: (i) any invasive breast cancer diagnosed prior to the commencement of screening or an invasive breast cancer diagnosed outside of the screening program after 24 months have elapsed following a negative screening episode; or (ii) an invasive breast cancer diagnosed in a woman who had not participated in an organised screening program.

Geographic remoteness of residence was categorised by an Accessibility-Remoteness Index of Australia Plus (ARIA+) classification, with the categories of Major City, Inner Regional, Outer Regional, Remote and Very Remote areas. Due to small numbers Remote and Very Remote categories were combined. These classifications are based on road distance from a locality to the closest service center (AIHW 2004).

Socio-economic status (SES) measured by Socio-Economic Indexes for Area (SEIFA) is based on the Index of Relative Socio-Economic Advantage and Disadvantage (IRSAD) calculated by the Australian Bureau of Statistics (Australian Bureau of Statistics 2008). This index was chosen because it does not include Indigenous status in its derivation. It provides a general measure of socio-economic disadvantage, with its scores collapsed into quintiles Q1 (most disadvantaged) to Q5 (most advantaged).

Population all-cause age-specific mortality rates were calculated from the unit record mortality file for Queensland residents, and generated for each combination of SLA, gender and broad time period (1997–2002; 2003–2007). To provide greater stability, mortality and population data for each SLA were combined with the relevant data from the neighbouring SLAs, as defined by the adjacency matrix. The expected number of deaths due to

any cause among the breast cancer cohort for each combination of variables was generated from these population mortality rates. Although these expected deaths include the effect of deaths due to breast cancer, this does not, in practice, affect the estimated survival proportions (Dickman *et al.* 2004).

### 2.3. Model specification

Following others such as Dickman *et al.* (2004) and Cramb *et al.* (2011b), and consistent with most modern survival analyses on population-based cancer data, a relative survival model was used. This has the advantage of not requiring cause of death information among the breast cancer cohort (Dickman *et al.* 2004; Pohar & Stare 2006; Fairley *et al.* 2008; Cramb *et al.* 2011b).

To model the observed number of deaths a generalized linear model with a Poisson assumption was used:

$$d_\epsilon \sim \text{Poisson}(\mu_\epsilon),$$

where  $d_\epsilon$  is the observed number of deaths due to any cause among the cohort of breast cancer patients for each stratum ( $\epsilon$ ), and  $\mu_\epsilon$  is the mean of the observed number of deaths due to any cause.

For a relative survival model that measures the relative excess risk (RER), the mean of the observed number of deaths ( $\mu_\epsilon$ ) can be modelled by

$$\mu_\epsilon = d_\epsilon^* + y_\epsilon \times \exp(\eta_\epsilon),$$

where  $d_\epsilon^*$  is the expected number of non-breast cancer deaths among the cohort of breast cancer patients for each stratum ( $\epsilon$ ). The person-time at risk,  $y_\epsilon$ , is the total amount of time in each year that the study subjects are at risk of dying from breast cancer, and  $\eta_\epsilon$  represents the excess hazard. The subscript  $\epsilon$  is the general indicator for the partition of data including, as appropriate, time  $t$ , the spatial unit  $i$ , and the covariates described in Section 2.2 (and shown in Table 1).

The exponentiated values of the individual  $\eta_\epsilon$  components provide the RER for the corresponding model variables (e.g.  $\exp(\alpha)$ ,  $\exp(\beta)$  and  $\exp(u_i + v_i)$ ). The excess hazard ( $\eta_\epsilon$ ) is estimated by

$$\eta_\epsilon = \alpha_t + \beta x + u_i + v_i,$$

where  $\beta$  is the coefficient vector associated with the vector of predictor variables  $x$  listed in Section 2.2 as well as interactions between detection method and geographic location;  $\alpha_t$  is the  $t$ th intercept that varies by follow-up interval (i.e. number of years from diagnosis to death or censoring) for  $t = 1, 2, \dots, 12$ ; and  $u_i$  and  $v_i$  represent the  $i$ th SLA ( $i = 1, 2, \dots, 478$ ) with spatially structured and unstructured random effects, respectively. The prior distribution for all entries of  $\beta$  and all  $\alpha_t$  is a zero mean Normal distribution with a  $\text{Gamma}(0.5, 0.005)$  hyperprior distribution for the precision;  $v_i$  is the geographic unstructured random effect and also has a zero mean Normal prior distribution with a  $\text{Gamma}(0.5, 0.005)$  hyperprior distribution for the precision; and  $u_i$  is the geographic structured random effect which has a conditional autoregressive (CAR) prior distribution (Besag, York & Molli 1991; Bell & Broemeling 2000; Banerjee, Wall & Carlin 2003; Best, Richardson & Thomson 2005; Earnest *et al.* 2007; Wakefield 2007). A CAR prior for  $u_i$  is of the form

TABLE 1

Number of eligible Queensland females diagnosed with breast cancer (1997–2007) and the percentage of those who died from any cause (1997–2008).

	All BC incidence (1997–2007)	All causes death (%) (1997–2008)
All Queensland women (0–89 years at diagnosis)	23,766	19.5
ARIA+		
Major City	14,464	19.0
Inner Regional	5066	20.1
Outer Regional	3351	20.3
Remote/Very Remote	885	22.9
SES IRSAD		
Quintile 1 Most disadvantaged	2871	22.2
Quintile 2	5179	21.5
Quintile 3	6204	19.7
Quintile 4	5638	18.5
Quintile 5 Most advantaged	3874	16.2
Detection method		
Screening	6902	10.0
Interval	2843	14.5
Non-screen	14,021	25.2
Age (years)		
0–39	1428	16.4
40–49	4669	11.5
50–59	6443	12.4
60–69	5545	16.1
70–89	5681	38.3
Indigenous status		
Non-Indigenous	20,529	21.7
Indigenous	257	31.5
Indigenous status unknown	2980	3.8
Marital status		
Married	14,801	14.5
Never married	1441	21.3
Widowed/divorced/separated	6787	31.7
Marital status unknown	737	6.1
Tumour stage		
Localised	11,517	10.8
Advanced	10,699	23.7
Stage unknown	1550	55.4

Notes: ARIA+, accessibility-remoteness index of Australia plus; IRSAD, index of relative socio-economic advantage and disadvantage; SES, socio-economic status.

$$u_i | u_{(-i)} \sim \text{Normal} \left( \frac{\sum_j w_{ij} u_j}{w_{i+}}, \frac{\sigma_u^2}{w_{i+}} \right)$$

$$w_{i+} = \sum_j w_{ij},$$

where  $u_{(-i)}$  denotes the value of the  $u$  variate in all areas except the  $i$ th area. The  $w_{ij}$  is the  $ij$ th element of a symmetric  $n \times n$  ‘weight’ matrix  $\mathbf{W}$  with diagonal elements  $w_{ii} \equiv 0$ . We choose  $w_{ij} = 1$  if locations  $i$  and  $j$  are neighbours and  $w_{ij} = 0$  otherwise, hence  $w_{i+}$  is equal to the number of neighbours of location  $i$ . The neighbourhood matrices of Queensland from Cramb *et al.* (2011b) were applied to the CAR prior distribution in our models.

## 2.4. Computation

The Bayesian hierarchical models were estimated using R (R Development Core Team 2011) and WinBUGS (Lunn *et al.* 2000). The R program was used to handle data manipulation prior to running the model, and to analyse the posterior densities of the model parameters. WinBUGS was used to perform MCMC to produce the posterior samples. Each model was run with two chains until convergence (total iterations ranged from 100,000 to 150,000) and 30,000 simulated samples were retained for inference.

Convergence checks for model parameters employed in R included the Gelman & Rubin (1992) convergence diagnostic, trace plots, density plots and autocorrelation plots.

## 2.5. Model fitting and evaluation

Models were fitted to answer the three research questions. In order to answer the first question (Q1), three models were fitted (M1\_1, M1\_2 & M1\_3), each including the demographic and stage variables. In addition, Model 1 included remoteness, Model 2 included area disadvantage and Model 3 included both remoteness and disadvantage. For the second question (Q2), the models from question 1 (M1\_1 to M1\_3) were re-fitted with the addition of detection method (M2\_1 to M2\_3). For the last question (Q3), the M2 models were extended by adding the interaction between the detection method and the geographic variables to each model (M3\_1 to M3\_3). Several other models were fitted outside the scope of the three questions. One such model, which consisted of all the demographic, stage and detection method variables (M0\_2), was used to assess the spatial variability or inequalities of relative survival among breast cancer patients in Queensland.

The posterior predictive check (PPC) (Gelman *et al.* 2004) was used to assess how adequately the model represents the observed data. The assessment procedure is as follows. First, the expected value  $\mu$  is calculated using the posterior distribution of relevant parameters. Second, the expected data  $d$  are generated from a Poisson distribution using the estimated  $\mu$ , and a posterior predictive distribution is formed. Third, each observed  $d$  is then compared with the corresponding posterior predictive distribution to assess whether it is encompassed in the 95% credible interval (CI) of the distribution. An adequate model is often declared if around 95% of the observed data are within the 95% CI of the posterior predictive distribution.

The Deviance Information Criterion (DIC) was used to determine the preferred model, with lower values indicating a ‘better’ model (Gelman *et al.* 2004). DIC is calculated as the sum of the mean deviance and an estimate of the effective number of parameters (pD), with smaller deviance indicating better fit, and smaller pD values indicating less complexity in the fitted model.

The posterior estimate of a relative survival model parameter is declared to be ‘sufficiently specific’ if the 95% CI of the corresponding exponentiated regression coefficient does not include the value ‘1’ (Wakefield 2007; Wu *et al.* 2010; Puigpins-Riera *et al.* 2011).

To assess the spatial variability within the model, disease maps of SLA-specific RER were generated and a numerical measure was calculated using the variance of the spatial random effects. The proportion of extra spatial variability was calculated as the ratio of the marginal spatial structured variance to the sum of the variance of both marginal spatial structured and unstructured random effects (Eberly & Carlin 2000; Saez *et al.* 2012).

### 3. Results

Table 1 gives the number of eligible women living in Queensland who had been diagnosed with breast cancer between 1997 and 2007, as well as the percentage of this cohort who had died from all causes up to 31 December, 2008.

The proportions of women who died from any cause during the study period were larger for women who resided in Remote or Very Remote areas, and those who lived in SLAs with a socio-economic status of quintile 1 or 2 (disadvantaged). The largest proportions of all cause mortality were observed in females whose breast cancer was detected outside a screening program (non-screen), women aged 70–89, Indigenous, widowed/divorced/separated as well as unknown tumour stage.

#### 3.1. Impact of patient demographics, stage and geographic location (Q1)

The selection of the final model was based on the effect of remoteness and area disadvantage. The final DIC values (with pD in brackets) for the three fitted models (M1\_1, M1\_2 & M1\_3) were 35641.1 (49.8), 35643.8 (53.3) and 35644.1 (53.5) respectively. Based on this, the final model (Table 2) was chosen to be the one that retained remoteness but excluded area disadvantage (M1\_1). There was very little difference in the RER estimates for the common variables across the three models (results not shown). Generally the RER increased for women living in rural/remote areas, oldest age group (70–89), Indigenous women, those who were not married at time of diagnosis, and those with an advanced or unknown stage tumour.

#### 3.2. Impact of detection method after adjusting for other factors (Q2)

The inclusion of detection method provided substantial improvement to the model fit with much smaller DIC values, as evidenced by models M0\_2 and M2\_3 in Table 2. The inclusion of geographic remoteness and disadvantage in model M0\_2 generated three models with similar DIC values that differ by less than 5 [M2\_1(remote): 35,455.4 (pD 48.8), M2\_2(disadvantage): 35,457.7 (57.3), M2\_3(remote & disadvantage): 35,458.0 (53.9)]. The model including both geographic remoteness and disadvantage (M2\_3) was selected to be the most appropriate model as it provided additional useful information (Table 2). Although models M0\_2 and M2\_3 had similar DIC and pD values, due to the additional geographical information model M2\_3 was preferred over M0\_2. The only significant change after including detection method was a reduction in RER among those aged 40–49 years. There remained higher RER for breast cancer patients residing in remote areas, disadvantaged regions, and those not participating in a screening program.

#### 3.3. Evidence for interactions (Q3)

Based on the DIC values [M3\_1: 35,462.5 (pD 56.3), M3\_2: 35,466.1 (62.4), M3\_3: 35,474.2 (70.4)], the preferred model with interactions included area remoteness, but not socio-economic status (Table 3). There was no visible change to the main effect results after including interaction terms. As interactions between the detection method and area remoteness fluctuated around the baseline value and were not sufficiently specific, a main effects only model was preferred over the interaction model.

TABLE 2

*RER of detection methods, demographic, tumour stage and geographic status for aged 0–89 Queensland female residents with breast cancer, 1997–2008.*

Factors	RER (95% CI)		
	Model M0_2	Model M1_1	Model M2_3
ARIA+			
Major City	—	1.00	1.00
Inner Regional	—	1.1208 (0.9643, 1.2710)	1.0957 (0.9578, 1.2420)
Outer Regional	—	1.1528 (0.8953, 1.3530)	1.1393 (0.9562, 1.3270)
Remote/Very Remote	—	1.4065 (1.0370, 1.7530)	1.3712 (1.0720, 1.6980)
SES IRSAD			
Quintile 1 Most disadvantaged	—	—	1.2060 (0.9971, 1.4430)
Quintile 2	—	—	1.1519 (0.9770, 1.3550)
Quintile 3	—	—	1.1698 (1.0030, 1.3610)
Quintile 4	—	—	1.0928 (0.9367, 1.2710)
Quintile 5 Most advantaged	—	—	1.00
Detection method			
Screening	0.4136 (0.3545, 0.4777)	—	0.4116 (0.3531, 0.4742)
Interval	0.7033 (0.6102, 0.8060)	—	0.7014 (0.6087, 0.7989)
Non-screen	1.00	—	1.00
Age (years)			
0–39	0.9159 (0.7776, 1.0690)	1.1563 (0.9821, 1.3490)	0.9127 (0.7740, 1.0630)
40–49	0.8243 (0.7273, 0.9322)	0.9128 (0.8046, 1.0320)	0.8230 (0.7241, 0.9291)
50–59	1.00	1.00	1.00
60–69	1.1332 (0.9979, 1.2780)	1.1244 (0.9901, 1.2710)	1.1282 (0.9930, 1.2720)
70–89	1.4869 (1.3140, 1.6770)	1.6122 (1.4250, 1.8140)	1.4835 (1.3170, 1.6720)
Indigenous status			
Non-Indigenous	1.00	1.00	1.00
Indigenous	1.8588 (1.4050, 2.3840)	1.8402 (1.3860, 2.3500)	1.7540 (1.3250, 2.2390)
Indigenous status unknown	0.0352 (0.0087, 0.0710)	0.0374 (0.0099, 0.0754)	0.0420 (0.0145, 0.0785)
Marital status			
Married	1.00	1.00	1.00
Never married	1.2791 (1.0890, 1.4830)	1.3140 (1.1190, 1.5310)	1.2878 (1.0990, 1.4920)
Widowed/divorced/ separated	1.3924 (1.2660, 1.5270)	1.4134 (1.2860, 1.5490)	1.3922 (1.2640, 1.5260)
Marital status unknown	0.4181 (0.1836, 0.7238)	0.4159 (0.1838, 0.7172)	0.4269 (0.2031, 0.7168)
Tumour stage			
Localised	1.00	1.00	1.00
Advanced	4.1156 (3.6040, 4.7000)	4.5599 (3.9830, 5.2240)	4.0447 (3.5230, 4.6150)
Stage unknown	13.612 (11.690, 15.770)	17.033 (14.600, 19.890)	13.358 (11.470, 15.520)
Spatial structured variance	0.0215 (0.0086, 0.0406)	0.0070 (0.0009, 0.0359)	0.0048 (0.0012, 0.0155)
Spatial unstructured variance	0.0070 (0.0014, 0.0219)	0.0077 (0.0017, 0.0227)	0.0079 (0.0016, 0.0237)
Extra spatial variability	0.7603	0.4387	0.3982
DIC	35,457.2	35641.1	35,458.0
pD	55.8	49.8	53.9
PPC	0.9853	0.9858	0.9855

Notes: ARIA+, accessibility-remoteness index of Australia plus; DIC, deviance information criterion; IRSAD, index of relative socio-economic advantage and disadvantage; PPC, posterior predictive check; RER, relative excess risk; SES, socio-economic status.

TABLE 3

*RER of interaction between detection methods and geographic factors for eligible Queensland female residents with breast cancer, 1997–2008.*

Model M3_1 Factors	RER (95% CI)		
	Main effect	Screening interaction	Interval interaction
<b>ARIA+</b>			
Major City	1.00	1.00	1.00
Inner Regional	1.1226 (0.9714, 1.2810)	1.0336 (0.7188, 1.4200)	1.0376 (0.7406, 1.3970)
Outer Regional	1.2471 (1.0150, 1.4590)	0.7671 (0.4827, 1.1200)	0.7867 (0.5172, 1.1330)
Remote/Very Remote	1.4252 (1.0790, 1.7980)	1.3027 (0.7101, 2.0980)	0.8675 (0.4358, 1.4570)
<b>SES IRSAD</b>			
Quintile 1 Most disadvantaged	—	—	—
Quintile 2	—	—	—
Quintile 3	—	—	—
Quintile 4	—	—	—
Quintile 5 Most advantaged	—	—	—
<b>Detection method</b>			
Screening	0.4218 (0.3460, 0.5058)	—	—
Interval	0.7340 (0.6020, 0.8780)	—	—
Non-screen	1.00	—	—
<b>Age (years)</b>			
0–39	0.9151 (0.7752, 1.0660)	—	—
40–49	0.8256 (0.7283, 0.9334)	—	—
50–59	1.00	—	—
60–69	1.1355 (1.0010, 1.2820)	—	—
70–89	1.4956 (1.3240, 1.6830)	—	—
<b>Indigenous status</b>			
Non-indigenous	1.00	—	—
Indigenous	1.7885 (1.3640, 2.2970)	—	—
Indigenous status unknown	0.0436 (0.0161, 0.0789)	—	—
<b>Marital status</b>			
Married	1.00	—	—
Never married	1.2926 (1.1010, 1.4990)	—	—
Widowed/divorced/ separated	1.3957 (1.2700, 1.5270)	—	—
Marital status unknown	0.4390 (0.2093, 0.7413)	—	—
<b>Tumour stage</b>			
Localised	1.00	—	—
Advanced	4.0809 (3.5720, 4.6740)	—	—
Stage unknown	13.457 (11.570, 16.690)	—	—
<b>Spatial structured variance</b>			
Spatial unstructured variance	0.0060 (0.0012, 0.0202)	—	—
Extra spatial variability	0.4344	—	—
DIC	35,462.5	—	—
pD	56.3	—	—
PPC	0.9855	—	—

Notes: ARIA+, accessibility-remoteness index of Australia plus; DIC, deviance information criterion; IRSAD, index of relative socio-economic advantage and disadvantage; PPC, posterior predictive check; RER, relative excess risk; SES, socio-economic status.

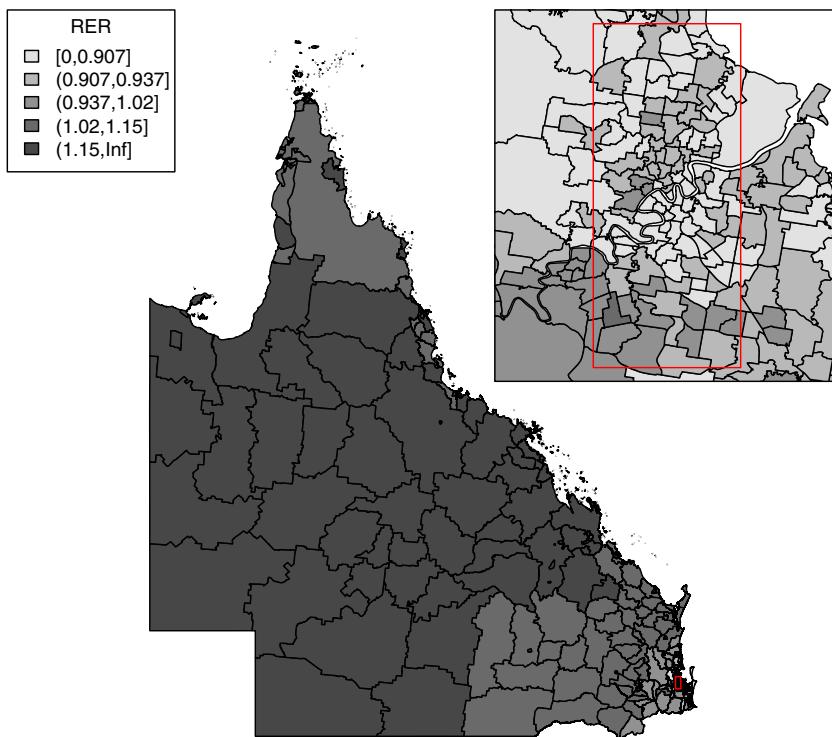


Figure 1. Posterior estimates of relative excess risk (RER) for each Statistical Local Area in Queensland & the southeast corner, based on Model M0\_2.

### 3.4. Spatial survival inequalities

Figure 1 presents a map of RER (divided into quintiles) in each SLA in Queensland and, in finer detail, the more populated southeast corner of the state, compared to the Queensland average RER (1), before including geographic remoteness and disadvantage (model M0\_2). There was evidence of spatial survival inequalities across Queensland SLAs (extra spatial variability = 0.76) with higher RER in northern and western Queensland and decreased RER of death in south-east Queensland. In Brisbane, smaller SLA-specific RER values were observed north of the Brisbane river and higher values south of the river. After including geographic remoteness and disadvantage in the analysis (model M2\_3), Figure 2 (using the same RER quintile categories as model M0\_2) demonstrates a visible reduction in spatial survival inequalities (extra spatial variability = 0.40).

## 4. Discussion

By applying a Bayesian spatial relative survival model to a large population-based cohort of Queensland women diagnosed with breast cancer, we have reinforced recent findings showing that participating in mammographic screening is associated with better breast cancer survival (Shen *et al.* 2005; Berry, *et al.* 2005, 2006; Bordas *et al.* 2007; Wishart *et al.* 2008; Wu *et al.* 2010; Mook *et al.* 2011; Nagtegaal *et al.* 2011; Nickson

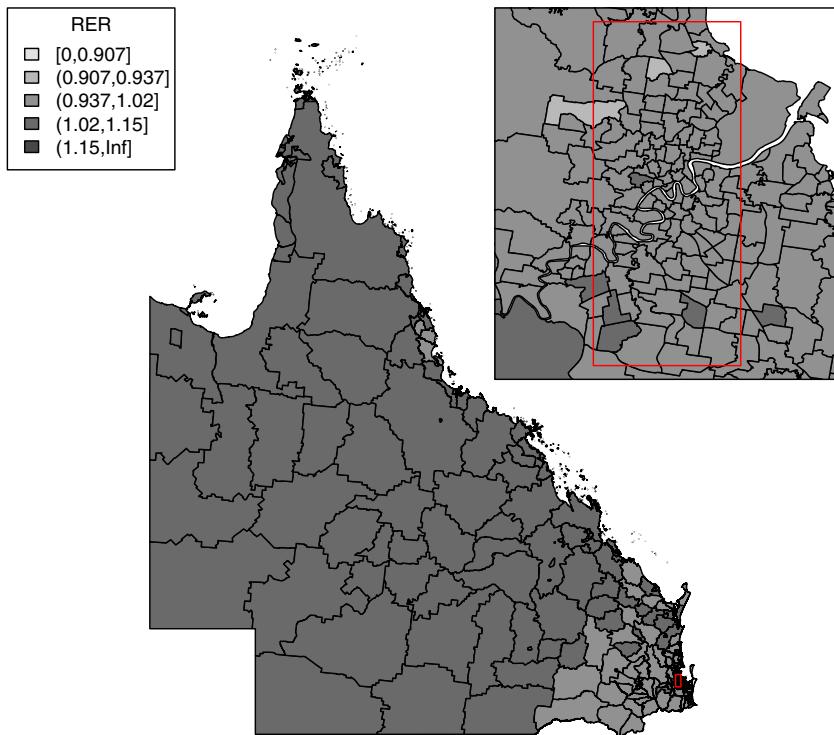


Figure 2. Posterior estimates of relative excess risk (RER) for each Statistical Local Area in Queensland & the southeast corner, based on Model M2\_3.

et al. 2012; Roder & Olver 2012). Importantly, this study demonstrated that there was no discernible evidence that this impact of breast cancer screening on survival varied by the women's geographical location, even after accounting for the extent of small area variation, tumour stage at diagnosis and other important demographic variables.

The survival advantage that we found for screen-detected cancers does need to be considered in light of the propensity for overdiagnosis in screening programs, in that asymptomatic cancers detected through population screening may not progress to cause symptoms, morbidity or subsequent death, and so would artificially increase the observed survival (Wishart et al. 2008; Barratt & Glasziou 2012; Bell & Burton 2012). However, we found that the survival benefit in participating a screening program was only marginally reduced after adjusting for tumour stage at diagnosis, demonstrating that earlier diagnosis did not explain the survival differential. While we have adjusted for a broad measure of tumour stage at diagnosis, there remains the possibility that some lead-time bias may be unaccounted by not having more detailed stage information. In addition, the lack of clinical information on the aggressiveness of the cancer restricted our ability to completely adjust for the effect of length bias, which reflects the propensity for screening programs to detect a disproportional number of slowly growing tumours (Shen et al. 2005). Thus it is possible that some of the observed association between screening and survival in our study could be explained by residual length bias, or, to a smaller extent, lead-time bias.

In addition, our finding that breast cancers diagnosed through population-based mammography screening have a two-fold survival advantage is consistent with the direction and strength of the effect reported by those case control studies that have used mortality as the end-point. A recent study in Western Australia and meta analysis of mammographic screening and breast cancer mortality (Nickson et al. 2012) reported that there was a 49% reduction in breast cancer mortality for women who were screened. This reduction was consistent across a range of studies covering five countries (Palli et al. 1989; Miltenburg et al. 1998; Fielder et al. 2004; Gabe et al. 2007; Allgood et al. 2008; Puliti et al. 2008; Roder et al. 2008; van Schoor et al. 2011; Otto et al. 2012).

However we found no evidence that the strong and beneficial impact of screening on breast cancer survival outcomes varied by geographic location for area disadvantage or remoteness. In contrast to the reported lower rates of Prostate Specific Antigen testing for prostate cancer among men living in rural areas of Australia (Baade et al. 2011b), breast screening participation rates have been reported to be slightly higher in rural and remote areas than in urban areas (Youlden, Cramb & Baade 2009). These results are encouraging, and reinforce the priority given to rural and remote areas of the state by BreastScreen Queensland to offset the barrier of distance by providing mobile screening vans, in addition to re-locatable and satellite services.

The impact that socio-demographic factors had on breast cancer survival in our study was consistent with that reported previously in a multilevel analysis of breast cancer survival in Queensland (Dasgupta et al. 2012) and other related studies (Condon et al. 2005; Shen, et al. 2005, 2007; Wishart et al. 2008; Cramb, et al. 2011a, 2012). That these independent associations held within a different methodological framework reinforce the need to identify ways to reduce the survival inequalities, particularly among indigenous women, older women and those who are not married. The estimated RER for age at diagnosis varied slightly when method of detection was added into the analysis, with poorer survival among younger women reversing to better survival after adjustment. One explanation of this could be that these cancers are generally symptomatic (Yankaskas 2006; Anders et al. 2008; Axelrod et al. 2008; Baade et al. 2011a) and not detected via screening (since the target age for breast screening is 50–69 years). This explanation is reinforced by the results, in that when the effect of screening is taken into account, younger women actually have slightly better adjusted survival.

One of the unique features of the Bayesian spatial methodology is the use of spatial random effects to accommodate possible spatial variation in the data. The majority of research investigating breast cancer screening has ignored the spatial location of cases, and the presence of any spatial correlation (Shen et al. 2005; Berry et al. 2006; Wishart et al. 2008; Mook et al. 2011; Nagtegaal et al. 2011; Bell & Burton 2012; Roder & Olver 2012). Inclusion of the random effect components enables a more realistic estimate of the RER in each SLA location and a better model fit (Besag et al. 1991; Best et al. 2005; Saez et al. 2012). Information from the random effect components can also be used to quantify and understand the spatial variation within the model, and how this varies between models. The disease maps also facilitate the visualization of spatial survival inequalities across the study regions, after adjusting for different health-related factors (Cramb et al. 2012).

Strengths of this study include the use of a large, unselected, population-based cohort of Queensland females diagnosed with breast cancer, with corresponding information about screening practices obtained from prospectively collected administrative data, the

collection of which was designed independently of the study, thus removing information bias. The Bayesian spatial relative survival models were able to accommodate the sparse area-specific data by borrowing information from neighbouring regions to smooth the estimated spatial random effects and directly quantify the estimate of spatial variation. By focusing on relative survival we were not constrained by any potential inaccuracies in the cause of death information.

We were not able to obtain information about mammography screening offered by private hospitals and practices. However the proportion of private mammography screens has been estimated to be very low, at between 1–4% (Australian Government Department of Health and Ageing 2012; Nickson *et al.* 2012). Therefore, by placing the privately screened women in the unscreened group, the true screening differential should not be badly underestimated.

This study has demonstrated a clear survival benefit in respect of breast cancers detected through mammographic screening among women aged less than 90 years at diagnosis, and that this benefit was consistent after adjusting for spread of disease and diagnosis. We found no substantive evidence that the screening benefit varied according to geographic location of residence. However since women diagnosed with breast cancer while living in rural and remote areas of Queensland are at higher risk of being diagnosed with advanced disease (Baade *et al.* 2011a), and since this explains much of the poorer survival outcomes in these areas (Dasgupta *et al.* 2012; Cramb *et al.* 2012) there remains an urgent need to increase screening and treatment participation among women in rural, remote and disadvantaged areas to reduce the current survival inequalities.

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