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ABSTRACT

Objectives: To investigate between-hospital variation in the probability of reoperation within 90 days of initial breast conserving surgery (BCS), and the contribution of health system-level and other factors.

Design: Population-based, retrospective cohort study.

Setting: New South Wales (NSW), Australia.

Participants: Linked administrative hospitalisation data were used to define a cohort of adult women undergoing initial BCS for breast cancer in NSW between 1 July 2002 and 31 December 2013.

Primary outcome measures: Multilevel, cross-classified models with patients clustered within hospitals and residential areas were used to examine factors associated with any re-operation, and either re-excision or mastectomy, within 90 days.

Results: Of 34,458 women undergoing BCS, 29.1% underwent reoperation within 90 days, half of which were mastectomies. Overall, the probability of reoperation decreased slightly over time. However, there were divergent patterns by reoperation type; the probability of re-excision increased alongside a concomitant decrease in the probability of mastectomy. Significant between-hospital variation was observed. Non-metropolitan location and surgery at low-volume hospitals were associated with a higher overall probability of reoperation, and of mastectomy specifically, after accounting for patient-level factors, calendar year and area-level socioeconomic status. The magnitude of association with geographic location and surgical volume decreased over time.

Conclusions: Reoperation rates within 90 days of BCS varied significantly between hospitals. For women undergoing mastectomy after BCS, this represents a dramatic change in clinical course. Multilevel modelling suggests that unwarranted clinical variation, likely due to disparities in access to specialist multidisciplinary breast cancer surgical care, may be an

issue. Improvement over time provides ongoing support for policy initiatives aimed at regionalisation.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The primary strength of this study is the use of best-practice multi-level modelling to investigate health-system level factors associated with reoperation after breast conserving surgery.
- One limitation is the lack of detailed information on tumour characteristics known to contribute to margin status.
- Another limitation is the inability to incorporate patient or surgeon perspectives which may have influenced surgical decisions.

INTRODUCTION

Clinical practice guidelines recommend that, where appropriate, women with early-stage breast cancer be offered either breast conserving surgery (BCS) with radiotherapy, or mastectomy.[1 2] Survival following BCS and radiotherapy is comparable to that following mastectomy. [3] However, BCS is associated with fewer post-operative complications [4] and improved quality of life. [5] In Australia, between 60-80% of women with early-stage breast cancer choose BCS,[6-8] with similar figures reported in the United States.[9]

However, a number of women who undergo BCS require reoperation, either re-excision or completion mastectomy.[10 11] This causes pain, suffering and anxiety, and may result in poorer cosmetic outcomes[12] and higher rates of recurrence due to delays in commencing adjuvant therapy.[13] The financial costs of reoperation are also considerable.[14] Population-based studies in the United States[10] and England[11] estimate the rate of reoperation ranges between 20-30%, though recent data suggest a downtrend in rates following the dissemination of clinical guidelines regarding surgical margins.[15] Previous Australian data are limited; a rate of 30% was estimated based on linked registry from Western Australia, 1998-2000.[8]

Factors associated with reoperation can be broadly divided into patient-level sociodemographic and clinical factors, together with health system-level factors.[16] Comprehensive investigation into health-system factors, which are potentially modifiable, is lacking, with few large population-based studies conducted,[8 10 11 17] only one of which[10] used best-practice multilevel modelling techniques to capture health system-level variation. If confirmed, variation in reoperation rates related to health system, rather than patient-level factors, has important policy and practice implications. We present multilevel, cross-classified models examining patient-level, area-level contextual and health system-level factors associated with reoperation following BCS for breast cancer in a statewide, population-based cohort of women from New South Wales (NSW), Australia, 2002-2013.

METHODS

Data sources and study population

The NSW Admitted Patient Data Collection (APDC) records inpatient separations from all hospitals in NSW. Patient demographics, together with principal and secondary diagnoses and procedures are recorded for each separation. Diagnoses are coded according to the International Statistical Classification of Diseases and Related Problems, 10th Revision, Australian Modification, (ICD-10-AM) and procedures according to the Australian Classification of Health Interventions (ACHI). The NSW Registry of Births, Deaths and Marriages (RBDM) records all deaths registered in NSW. An extract of the NSW APDC containing records between 1 July 2001 and 31 March 2014 was linked with the NSW RBDM by the NSW Centre for Health Record Linkage (http://www.cherel.org.au/) using an established probabilistic linkage method. Ethical approval was obtained from the NSW Population and Health Services Research Ethics Committee and the NSW Aboriginal Health and Medical Research Council Ethics Committee.

These data were used to define a cohort of adult (≥16 years) women with a diagnosis of invasive (ICD-10-AM C50) or insitu (ICD-10-AM D05) breast cancer who underwent initial BCS in NSW hospitals between 1 July 2001 and 31 March 2014, based on either principal or secondary diagnosis and procedure codes (n=39,255). We excluded women whose initial BCS occurred prior to 1 July 2002 (n=3,070); this ensured a lookback period of at least 12 months in which to assess record of previous breast or other cancer, and comorbidities. Similarly, we excluded women with less than 90 days follow-up after their initial BCS (n=896), either because it occurred after 31 December 2013, or they died within 90 days. We also excluded women who were not permanent residents of NSW (n=831). This left a final analytical cohort of n=34,458 women (Figure 1).

BCS was defined by ACHI procedure codes for excision of lesion of breast (includes excisional biopsy), local excision of lesion of breast, segmental resection of breast, and partial mastectomy (see Online Resource 1 for codes). Breast reoperation was defined by procedure codes for re-excision or mastectomy within 90 days of initial BCS. A period of 90 days was applied to avoid including reoperations for local recurrence. Open (incisional) biopsy (30344-00, 31500-01) was not considered BCS. In women undergoing both re-excision and mastectomy following BCS, mastectomy was taken as the definitive procedure.

Explanatory variables

Patient-level sociodemographic variables at initial BCS included: age-group; Australian Aboriginal or Torres Strait Islander status (hereafter referred to as 'Aboriginal'); and, country of birth. Patient-level clinical variables included: invasive or insitu tumour type; previous breast cancer recorded up to 12 months prior to initial BCS; and, other previous cancer and comorbidities (defined as per Charlson[18]), recorded either at admission for initial BCS or up to 12 months prior. Previous breast cancer was assigned only where it could be determined that the record was not related to the diagnosis of, or neoadjuvant treatment for, the current breast tumour. Calendar year of initial BCS was also included.

Patient-level socioeconomic status is not recorded on the APDC; however, the Index of Relative Socioeconomic Disadvantage (IRSD, quintiles) was included as an area-level contextual variable, based on statistical local area of residence (SLA) defined using boundaries from the 2006 Australian Census.[19] SLAs are one of the smallest geographic units available in the Australian Standard Geographical Classification, with 199 across the status of NSW (average population 32,859, range 346-133,837).[20]

Health system-level variables at initial BCS included hospital identifier, public or private hospital type and BCS surgical volume (<15, 15-49, 50+), based on the average annual

number of BCS cases. Categorisation of BCS surgical volume was informed by visual inspection of its distribution [not shown]. Geographic remoteness (metropolitan, non-metropolitan) was defined according to the Accessibility/Remoteness Index of Australia,[20] and categorised as the combination of residential and hospital location, in order to capture differences in access to specialist, multidisciplinary inpatient breast cancer care, as well as outpatient services, such as mammographic screening and preoperative diagnosis. While the majority (95.3%) of women living in metropolitan areas underwent initial BCS in metropolitan hospitals, only 72.1% of women living in non-metropolitan areas were treated in non-metropolitan hospitals [data not shown elsewhere].

Statistical analysis

Multilevel, cross-classified logistic regression models were used to examine the probability of reoperation versus no reoperation (binomial) and re-excision or mastectomy versus no-reoperation (multinomial) within 90 days of initial BCS; supplementary binomial modelling examining the probability of mastectomy versus re-excision was also performed. Individuals were treated as the unit of analysis, and were clustered according to both the hospital in which their initial BCS was performed and their SLA of residence, using cross-classified random intercept parameters. Variation in the probability of reoperation between hospitals and between SLAs was quantified using the variance of the random intercept parameters.[21]

Baseline models included the random intercepts for hospital and SLA, and age-group at initial BCS, with subsequent models sequentially adding other patient-level sociodemographic and clinical variables, calendar year, area-level contextual and health system-level variables. Adjusted odds ratios (ORs) were obtained by exponentiating the regression parameters. Population-averaged, predicted probabilities of reoperation (expressed as a percentage) were also estimated from the fitted model. We examined whether the association between health

system-level factors and the probability of reoperation varied over time by separately including interaction terms between geographic location, BCS surgical volume and calendar year of initial BCS in the corresponding main effect model.

All data preparation was performed in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), and all modelling in MLwiN version 2.35 (Browne et al., Centre for Multilevel Modelling, University of Bristol). For all statistics, *p*-values were two-tailed, and alpha was set at 0.05.Models were fitted using Markov Chain Monte Carlo (MCMC) estimation with inference based on 20,000 samples following a burn-in of 5,000. Trajectories of stored parameter estimates were visually checked for irregular distributions and convergence to a unimodal distribution.

RESULTS

Cohort characteristics

Between 1 July 2002 and 31 December 2013, 34,458 women with breast cancer underwent initial BCS in 161 NSW hospitals. The median age at initial BCS was 59 years (interquartile range 50-67 years). The majority (68.9%) of women were born in Australia/New Zealand, and 0.9% identified as Aboriginal (Table 1). Most women had invasive tumours, with 26.6% having insitu tumours, or tumours with an insitu component; of these tumours n=6,377 (69.6%) were DCIS [data not shown elsewhere]. A small proportion (0.7%) of women had previous breast cancer, 0.8% had another cancer, and 8.0% had comorbidities recorded in hospital admissions data at or within 12 months of initial BCS. Most women (69.5%) both resided and underwent initial BCS in metropolitan areas. Over half (55.0%) attended private hospitals and a similar figure attended high-volume hospitals (≥50 BCS cases per year). Women undergoing BCS in non-metropolitan hospitals were significantly less likely to have attended a private or high-volume hospital (see Online Resource 2 for cross-tabulation).

As shown in Table 2, 10,018 (29.1%) of women underwent at least one reoperation within 90 days of initial BCS, either re-excision (n=5,146, 14.9%) or mastectomy (n=4,872, 14.1%). Of women undergoing mastectomy, 15.8% had also undergone re-excision (see Online Resource 3 for flow diagram). The proportion of women undergoing reoperation decreased slightly over time, from 30.1% to 27.8%. Divergent patterns were observed by reoperation type; the proportion of women undergoing re-excision increased over time, from 12.8% in 2002-2005 to 15.9% in 2010-2013, whereas the proportion of women undergoing completion mastectomy decreased from 17.2% to 11.9%.

Multilevel modelling

The population-averaged predicted probability of reoperation was 28.2%, with estimates of 14.6% and 13.4% for re-excision and mastectomy respectively (Table 2). Significant variation was observed between hospitals in the overall probability of reoperation, as well as for re-excision and mastectomy, in both baseline and adjusted models (see Online Resource 4 for variance). Significant variation was also observed between residential SLAs, though this was notably smaller than the variation seen between hospitals.

A clear pattern emerged for some explanatory factors (Table 2; Online Resources 5-6). The probability of reoperation, whether by re-excision or mastectomy, was consistently higher among women of East Asian origin and those with insitu tumours, and was consistently lower for women with a previous breast cancer. The probability of reoperation was consistently higher among younger women compared with women aged 50-64 (the target age group for mammographic screening in Australia) and lower among older women; women undergoing reoperation in these age groups were significantly more likely to undergo mastectomy than re-excision. There was no association between reoperation and other previous cancers, the number of comorbidities, area-level socioeconomic status, or public or private hospital type.

For other factors, there were notable differences in the pattern of reoperation by re-excision or mastectomy (Table 2; Figure 2; Online Resources 5-6). As per the descriptive analyses, there was a decrease in the overall probability of reoperation over time, however, divergent patterns were observed; the probability of re-excision increased alongside a concomitant decrease in that for mastectomy. Women attending lower-volume hospitals had a higher overall probability of reoperation compared with those attending higher-volume (≥15 BCS cases per year) hospitals. Women living in non-metropolitan areas and who attended non-metropolitan hospitals had a higher overall probability of reoperation than those living in metropolitan areas and who attended metropolitan hospitals. Both these associations were seen for mastectomy, but not for re-excision. Significant interactions were observed between the effect

of year of initial BCS and each of geographic location (p<0.001) and volume (p=0.008) on the probability of mastectomy, with the magnitude of the differences reducing over time (Figure 3). There was no difference in the overall probability of reoperation by indigenous status, although Aboriginal women had a higher probability of mastectomy than non-Aboriginal women, based on small numbers.

DISCUSSION

In this statewide, population-based study of women undergoing initial BCS for breast cancer in Australia during 2002-2013, 29.1% underwent reoperation within 90 days, almost half undergoing mastectomy. Significant between-hospital variation was observed. Overall, the probability of reoperation decreased slightly over time. However, there were divergent patterns by reoperation type; the probability of re-excision increased alongside a concomitant decrease in the probability of mastectomy. Women living in non-metropolitan areas and who attended non-metropolitan hospitals, as well as those attending low-volume hospitals, had a higher probability of reoperation, particularly mastectomy, even after adjusting for patient- and area-level contextual factors. The magnitude of association with geographic location and volume decreased over time.

This is the first study to have used multilevel modelling to thoroughly investigate the role of health system-level, area-level contextual and patient-level factors in reoperation following BCS. It is also the first to have applied multilevel multinomial modelling to separately examine factors associated with re-excision and mastectomy; this is important, as some associations were obscured when examined for all reoperations combined, in a demonstration of Simpson's paradox.[22]

This is one of few published population-based studies. NSW hospitalisation data have been demonstrated to have high sensitivity and specificity in identifying breast cancer patients when validated against cancer registry data,[23] and to provide unbiased estimates of BCS.[24] However, the potential for miscoding within administrative datasets is acknowledged. Further, due to inherent characteristics of ICD-10-AM diagnostic codes, it is not possible to distinguish excisional biopsies performed for diagnostic purposes from those performed with the intention of complete excision.[8] We were unable to account for laterality. However, the availability in ICD-10-AM of a diagnostic code specific for re-excision and the low likelihood

of contralateral mastectomy within 90 days of BCS means that any misclassification of reoperation due to absence of data on laterality would be minimal. We could not consider margin status, nor fully account for stage, histology and other tumour characteristics known to contribute to margin status. However, it is unlikely that variation based on these factors would have accounted for the hospital variation we observed. Finally, we could not incorporate patient or surgeon perspectives; the complexities of decision-making in the surgical treatment of breast cancer cannot be adequately assessed using administrative data.[8]

Our observed overall reoperation rate is similar to that for contemporaneous, population-based cohorts in the United States (New York, 2002-2013; 31%)[10] and the Netherlands (Rotterdam, 2006-2007; 29%)[25] but higher than that from the United Kingdom (England, 2005-2008; 20%).[11] Lower rates were reported from Spain (Catalonia, 2005-2011; 12%)[26] and Ireland (2002-2008; 17%)[17] but these studies did not include DCIS.

Variability in reoperation rates can be partly explained by differences in approach to surgical margins. Reoperation primarily occurs due to positive or negative close margins.[27] Historically, there has been lack of consensus on what constitutes an adequate negative margin,[28 29] though in the context of multimodality breast cancer treatment, wider margins are no longer superior in terms of local recurrence.[15] Consensus guidelines were recently published recommending 'no ink on tumour' as an adequate surgical margin for patients with early-stage invasive breast cancer undergoing BCS with radiotherapy (2014)[30] and 2mm for DCIS (2016).[31] This fundamental shift in approach is reflected in our observation of changing proportions of women undergoing re-excision and mastectomy over time, also noted in the New York cohort,[10] and in recent analyses of United States Surveillance, Epidemiology and End Results registry data.[15]

Between-hospital variation in reoperation rates has not been previously demonstrated using multilevel analyses. Variability in reoperation rates between surgeons was observed in the New York cohort,[10] as well as in a multi-site cohort of United States' breast cancer patients, though this study was not population-based.[32] Surgical volume, an accepted surrogate for specialisation, is one possible explanation.[10 17 25 27 32 33] Specialist breast cancer surgeons may be more proficient at obtaining negative margins, and less likely to re-excise close margins.[16] Patient selection and appropriateness of BCS as the initial treatment choice is also a factor. Anecdotal evidence suggests that treatment decisions made in high-volume hospitals are often made by multidisciplinary teams (MDTs), and differ from those made by clinicians working in isolation.[34]

Differences in the probability of reoperation, particularly mastectomy, between women living and undergoing treatment in metropolitan versus non-metropolitan areas potentially reflects differential access to specialist, multidisciplinary breast cancer care. A 2006 survey of Australian breast cancer surgeons showed, for example, that participation in MDTs is higher for surgeons in metropolitan than non-metropolitan areas.[35] Differential access to specialised radiological services able to perform localisation of impalpable lesions and intraoperative assessment to confirm complete excision may also be a valid consideration, as is access to preoperative diagnostic services.[8] Women in remote areas of Australia are less likely to have undergone preoperative diagnosis by fine-needle aspiration or core biopsy, and instead, more likely to have undergone surgical biopsy[36]; this may be exacerbated by lower rates of mammographic screening and referral for preoperative diagnosis.[37] Increased risk of reoperation could be expected therefore, as BCS may have been performed for diagnostic purposes rather than with the intention of complete excision.[8] This was evidenced in US surgical[32] and Medicare cohort data[33] where lack of preoperative diagnosis was associated with higher rates of reoperation.

Health system-level factors were found to be significant independent of patient-level factors, such as younger age,[8 10 11 17 27 38] and insitu tumour type.[10 11 38] Positive margins are more frequently observed in younger women, as smaller volumes of breast tissue are resected and tumours tend to have adverse histologic features.[39 40] In addition, preoperative diagnosis in younger women may be complicated by greater breast density and lower mammographic sensitivity.[40] Comparatively smaller breast size and greater breast density[41] may similarly account for the high probability of reoperation seen in Asian women.[38] Most (70%) insitu tumours in our cohort were DCIS. The margins of DCIS are less well defined than for invasive tumours, and extension into the breast tissue can be difficult to determine.[42] Hence, DCIS is more often associated with positive margins.[43 44] The higher probability of mastectomy seen among Aboriginal women should be interpreted cautiously due to small numbers, but nevertheless suggests they may be a high-risk group, independent of their place of residence. Aboriginal women in Australia have lower rates of screening participation,[37 45] disparate access to BCS,[7] and lower survival after breast cancer surgery.[45] Interestingly, we did not observe an association with area-level socioeconomic status, which has been related to differential access to BCS[7 46] and survival,[47] but not to differences in rates of screening.[37]

In summary, in a population-based cohort of Australian women, 29.1% underwent reoperation within 90 days of BCS, almost half undergoing mastectomy. For these women, this represents a dramatic change in clinical course. We used robust statistical methodology to show between-hospital variation in reoperation rates, and an association with health system-level factors, after considering patient- and area-level contextual factors. The association of BCS surgical volume and non-metropolitan location with mastectomy after BCS highlights the potential role of access to multidisciplinary, specialist breast cancer care in reducing unwarranted clinical variation. This is not unique to the Australian setting; a consensus conference held among the American Society of Breast Cancer Surgeons in 2015 advocated

several evidence-based recommendations to reduce variability in reoperation rates, including multidisciplinary care.[48] Disparities appear to have reduced, suggesting efforts to promote regionalisation of breast cancer care over the past decade may have had some success.[49 50]

AUTHOR CONTRIBUTIONS

All authors (MvL, MF, CV, PC, SL, EK, LJ, AS) made substantial contributions to the study concept and design. MvL had full access to the study data. MvL, CV, MF, and SL were responsible for developing the analytical protocol, and MvL and MF for executing the statistical analyses. All authors (MvL, MF, CV, PC, SL, EK, LJ, AS) made substantial contributions to the interpretation of the data. MvL, MF, and CV drafted the manuscript; all authors (MvL, MF, CV, PC, SL, EK, LJ, AS) revised it critically for important intellectual content. All authors (MvL, MF, CV, PC, SL, EK, LJ, AS) have approved the final version of the manuscript.

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COMPETING INTERESTS

The authors declare that they have no conflict of interest.

DATA SHARING

No additional data are available.

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TABLES

Table 1 **Patient-level, area-level contextual, and health system-level characteristics of women undergoing breast conserving surgery 2002-2013, NSW, Australia**

Variable	N (%)
Total cohort	34,458 (100.0)
Age (years)	
<35	579 (1.7)
35-49	7,308 (21.2)
50-64	15,209 (44.1)
65-79	9,309 (27.0)
80+	2,053 (6.0)
Aboriginal status	
Non-Aboriginal	34,161 (99.1)
Aboriginal	297 (0.9)
Country of birth	
Australia/New Zealand	23,746 (68.9)
Europe	4,863 (14.1)
East Asia	2,217 (6.4)
Other	2,808 (8.2)
Unknown	824 (2.4)
Tumour type	
Invasive	25,291 (73.4)
Insitu/insitu component	9,167 (26.6)
Previous breast cancer[a]	
No	34,211 (99.3)
Yes	247 (0.7)
Other previous cancer[1]	
No	34,169 (99.2)
Yes	289 (0.8)
Number of comorbidities[a]	
No comorbidities	31,689 (92.0)
1 comorbidity	2,303 (6.7)
2 comorbidities	348 (1.0)
3+ comorbidities	118 (0.3)
Year of initial BCS	
2002-2005	9,868 (28.6)
2006-2009	11,662 (33.8)
2010-2013	12,928 (37.5)
Index of relative socioeconomic disadvantage[b]	
Quintile 5 (Least disadvantaged)	12,319 (35.8)
Quintile 4	7,116 (20.7)
Quintile 3	6,860 (19.9)
Quintile 2	4,104 (11.9)
Quintile 1 (Most disadvantaged)	4,059 (11.8)

Variable	N (%)
Hospital type	
Public	15,516 (45.0)
Private	18,942 (55.0)
BCS surgical volume[c]	
<15	3,278 (9.5)
15-49	12,224 (35.5)
50+	18,956 (55.0)
Residential and hospital location	
Metropolitan x metropolitan	23,957 (69.5)
Metropolitan x non-metropolitan	2,602 (7.6)
Non-metropolitan x metropolitan	1,180 (3.4)
Non-metropolitan x non-metropolitan	6,719 (19.5)

Abbreviations: BCS, breast conserving surgery.
[a] Recorded on or within 12 months prior to initial BCS.
[b] Index of relative socioeconomic disadvantage for statistical local area of residence.
[c] Average annual number of BCS cases per hospital, 2002-2013.

Table 2 **Unadjusted and adjusted probabilities of any reoperation, and separately, of re-excision or mastectomy within 90 days of initial breast conserving surgery, NSW, Australia 2002-2013.[a]**

	Any reoperation		Reoperation (re-excision)		Reoperation (mastectomy)	
Variable	N	Unadjusted % (adjusted %)[a]	N	Unadjusted % (adjusted %)[a]	N	Unadjusted % (adjusted %)[a]
Total cohort	10,018	29.1 (28.5)	5,146	14.9 (14.6)	4,872	14.1 (13.4)
Age (years)						
<35	186	32.1 (32.6)	79	13.6 (13.3)	107	18.5 (18.8)
35-49	2,645	36.2 (35.6)	1,290	17.7 (17.1)	1,355	18.5 (18.0)
50-64	4,410	29.0 (28.4)	2,418	15.9 (15.5)	1,992	13.1 (12.5)
65-79	2,429	26.1 (26.1)	1,225	13.2 (13.2)	1,204	12.9 (12.5)
80+	348	17.0 (17.2)	134	6.5 (6.7)	214	10.4 (10.1)
Aboriginal status						
Non-Aboriginal	9,925	29.1 (28.5)	5,111	15.0 (14.4)	4,814	14.1 (13.3)
Aboriginal	93	31.3 (31.2)	35	11.8 (12.1)	58	19.5 (18.1)
Country of birth						
Australia/New Zealand	6,864	28.9 (28.0)	3,478	14.7 (14.6)	3,386	14.3 (13.4)
Europe	1,335	27.5 (28.4)	692	14.2 (14.4)	643	13.2 (13.9)
East Asia	776	35.0 (32.1)	406	18.3 (15.8)	370	16.7 (16.3)
Other	800	28.5 (28.2)	444	15.8 (14.8)	356	12.7 (13.3)
Unknown	243	29.5 (26.8)	126	15.3 (14.0)	117	14.2 (13.0)
Tumour type						
Invasive	6,557	25.9 (25.2)	3,404	13.5 (13.2)	3,153	12.5 (12.1)
Insitu/mixed	3,461	37.8 (37.6)	1,742	19.0 (19.1)	1,719	18.8 (18.5)
Previous breast cancer[b]						
No	9,973	29.2 (28.6)	5,125	15.0 (14.5)	4,848	14.2 (13.5)
Yes	45	18.2 (18.5)	21	8.5 (8.9)	24	9.7 (9.2)
Previous other cancer[b]						
No	9,951	29.1 (28.4)	5,117	15.0 (14.4)	4,834	14.2 (13.3)
Yes	67	23.2 (25.5)	29	10.0 (11.4)	38	13.2 (13.4)

Variable	Any reoperation N	Any reoperation Unadjusted % (adjusted %)[a]	Reoperation (re-excision) N	Reoperation (re-excision) Unadjusted % (adjusted %)[a]	Reoperation (mastectomy) N	Reoperation (mastectomy) Unadjusted % (adjusted %)[a]
Number of comorbidities[b]						
No comorbidities	9,357	29.5 (28.4)	4,836	15.3 (15.0)	4,521	14.3 (13.8)
1 comorbidity	557	24.2 (26.7)	268	11.6 (13.6)	289	12.6 (13.2)
2 comorbidities	84	24.1 (28.7)	33	9.5 (12.5)	51	14.7 (16.2)
3+ comorbidities	20	17.0 (22.0)	9	7.6 (11.1)	11	9.3 (10.9)
Year of initial BCS						
2002-2005	2,974	30.1 (29.4)	1,282	13.0 (12.3)	1,692	17.2 (16.0)
2006-2009	3,445	29.5 (29.4)	1,805	15.5 (15.0)	1,640	14.1 (13.4)
2010-2013	3,599	27.8 (27.7)	2,059	15.9 (15.3)	1,540	11.9 (11.4)
Index of relative socioeconomic disadvantage[c]						
Quintile 5 (Least disadvantaged)	3,656	29.7 (28.7)	1,955	15.9 (14.4)	1,701	13.8 (13.5)
Quintile 4	2,065	29.0 (29.2)	1,086	15.3 (14.8)	979	13.8 (13.5)
Quintile 3	1,957	28.5 (28.2)	942	13.7 (13.7)	1,015	14.8 (13.5)
Quintile 2	1,189	29.0 (29.1)	560	13.7 (14.6)	629	15.3 (13.6)
Quintile 1 (Most disadvantaged)	1,151	28.4 (29.4)	603	14.9 (15.3)	548	13.5 (13.2)
BCS surgical volume[d]						
<15	1,109	33.8 (32.1)	475	14.5 (14.8)	634	19.3 (16.8)
15-49	3,373	27.6 (27.3)	1,652	13.5 (14.0)	1,721	14.1 (12.9)
50+	5,536	29.2 (28.7)	3,019	15.9 (14.7)	2,517	13.3 (13.1)
Residential and hospital location						
Metropolitan x metropolitan	6,859	28.6 (27.7)	3,705	15.5 (14.7)	3,154	13.2 (12.6)
Metropolitan x non-metropolitan	425	36.0 (31.6)	236	20.0 (17.6)	189	16.0 (13.7)
Non-metropolitan x metropolitan	656	25.2 (27.4)	329	12.6 (13.7)	327	12.6 (13.2)
Non-metropolitan x non-metropolitan	2,078	30.9 (32.2)	876	13.0 (13.4)	1,202	17.9 (17.4)

Abbreviations: BCS, breast conserving surgery.

[a] Adjusted % (predicted probability) obtained from multilevel, cross-classified binomial (any reoperation) and multinomial (re-excision, mastectomy) logistic regression models, adjusted for patient-level factors, calendar year, area-level contextual factors, and health system-level factors.

[b] Recorded on or within 12 months prior to initial BCS.

[c] Index of relative socioeconomic disadvantage for statistical local area of residence.

[d] Average annual number of BCS cases per hospital, 2002-2013.

FIGURE LEGENDS

Figure 1 **Flow diagram showing study inclusion and exclusion criteria**

Figure 2 **Adjusted odds ratios for any reoperation versus no reoperation, and separately, for re-excision or mastectomy versus no reoperation within 90 days of initial breast conserving surgery, NSW, Australia, 2002-2013.** Shows ORs for calendar year and health system-level factors fully adjusted for patient-level and area-level contextual factors based on multilevel, cross-classified binomial (any reoperation) and multinomial (re-excision, mastectomy) logistic regression models.

Figure 3 **Population-averaged predicted probabilities of any reoperation, and separately, of re-excision or mastectomy, within 90 days of initial breast conserving surgery, by calendar year and location, NSW, Australia, 2002-2013.** Predicted probabilities obtained from fully adjusted multilevel, cross-classified binomial (any reoperation) and multinomial (re-excision, mastectomy) logistic regression models containing interaction terms between calendar year and geographic location. For illustrative purposes, graph restricted to concordant metropolitan or non-metropolitan residential and hospital location.

ONLINE RESOURCES

Online Resource 1	Australian Classification of Health Interventions (ACHI) procedure codes
Online Resource 2	Distribution of hospitals and patients by hospital type, surgical volume and hospital location
Online Resource 3	Flow diagram showing the number of women undergoing re-excision and mastectomy within 90 days of initial breast conserving surgery, NSW, Australia, 2002-2013
Online Resource 4	Area- and hospital-level variance (σ^2) and the proportional change in variance (%) between baseline and subsequent models, for any reoperation, and separately, for re-excision or mastectomy
Online Resource 5	Adjusted odds ratios for any reoperation versus no reoperation, and separately, for re-excision or mastectomy versus no reoperation within 90 days of initial breast conserving surgery, NSW, Australia 2002-2013
Online Resource 6	Adjusted odds ratios for mastectomy versus re-excision in women undergoing reoperation (n=10,018) within 90 days of initial breast conserving surgery, NSW, Australia 2002-2013

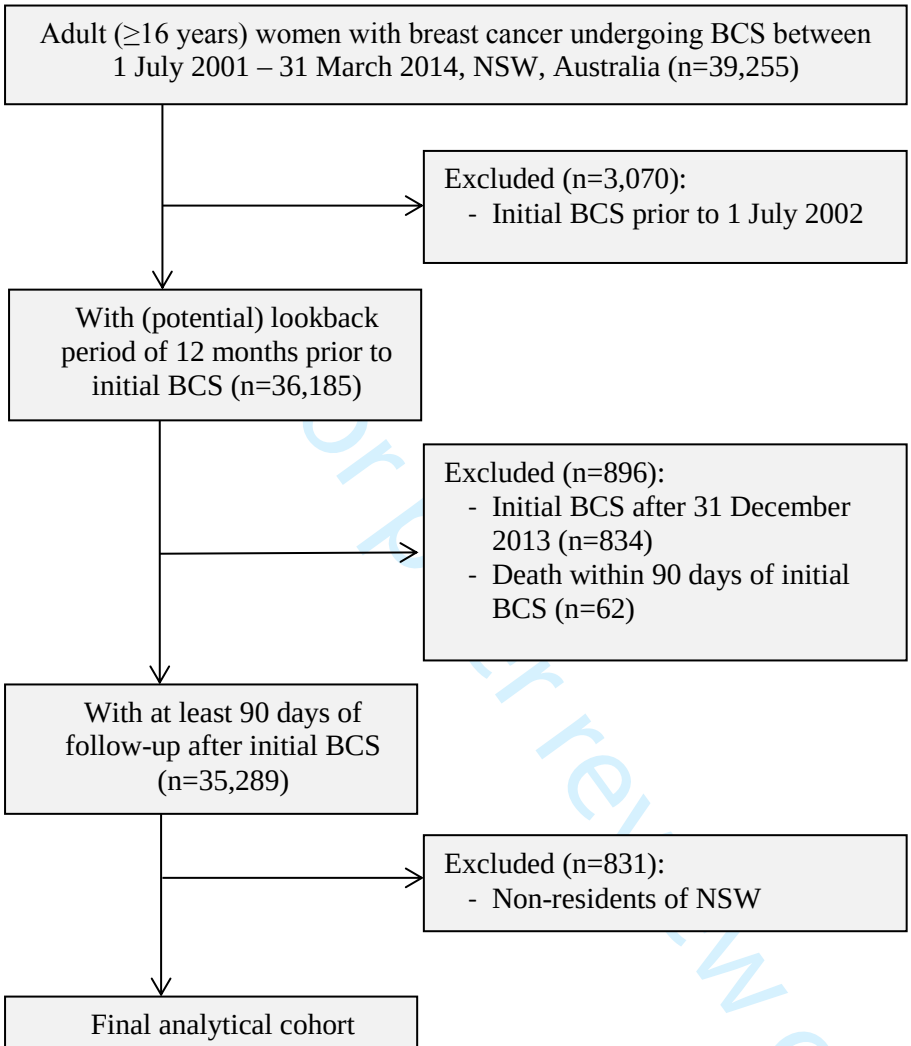
Adult (≥16 years) women with breast cancer undergoing BCS between 1 July 2001 – 31 March 2014, NSW, Australia (n=39,255)
Excluded (n=3,070):
- Initial BCS prior to 1 July 2002
With (potential) lookback period of 12 months prior to initial BCS (n=36,185)
Excluded (n=896):
- Initial BCS after 31 December 2013 (n=834)
- Death within 90 days of initial BCS (n=62)
With at least 90 days of follow-up after initial BCS (n=35,289)
Excluded (n=831):
- Non-residents of NSW
Final analytical cohort (n=34,458)

Figure 1

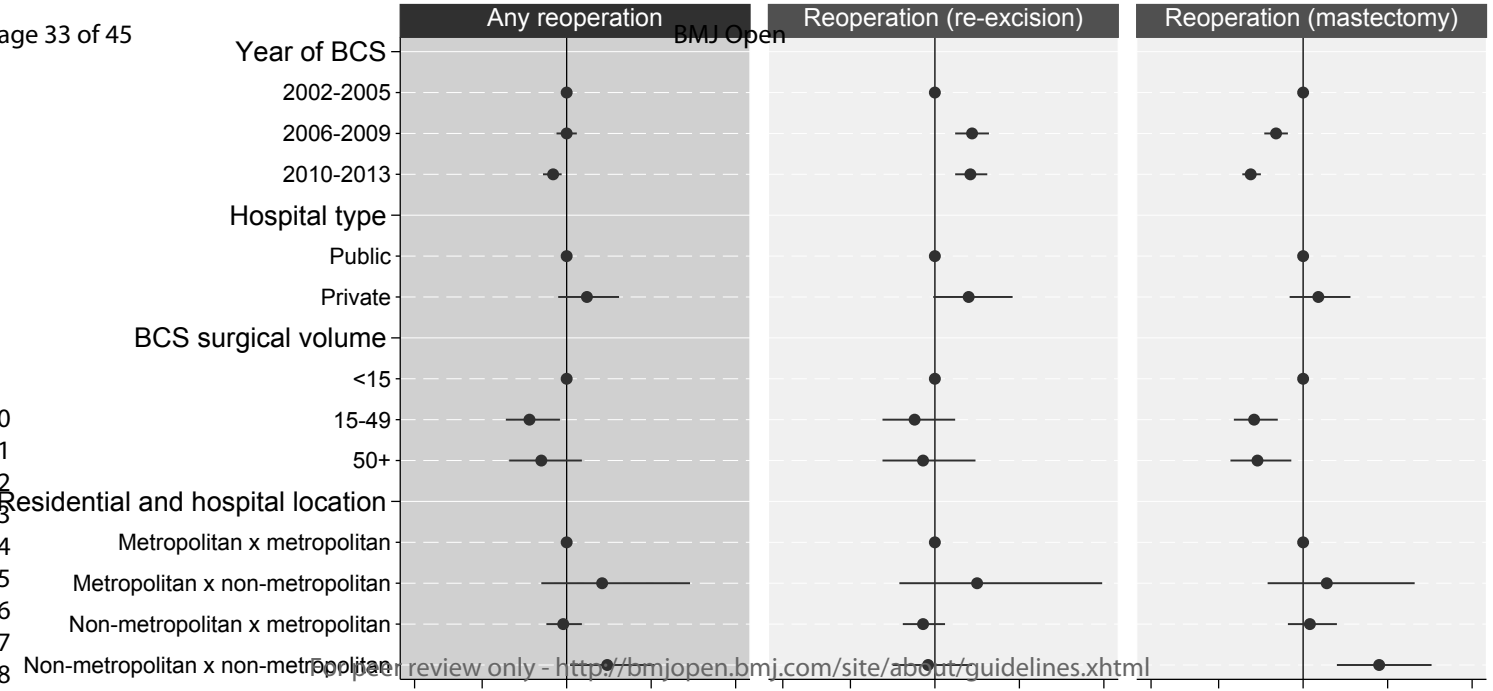

Figure 2

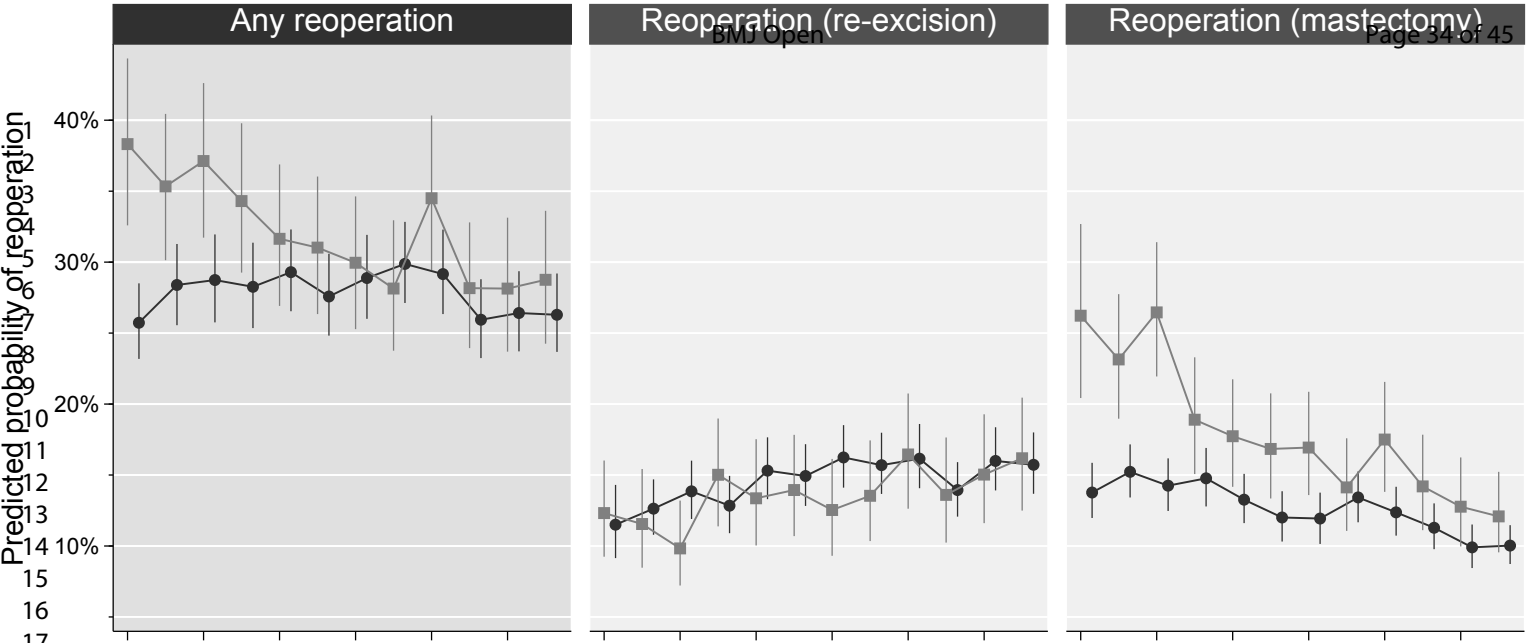

Figure 3

ONLINE RESOURCES

Online Resource 1	Australian Classification of Health Interventions (ACHI) procedure codes
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Online Resource 6	Adjusted odds ratios for mastectomy versus re-excision in women undergoing reoperation (n=10,018) within 90 days of initial breast conserving surgery, NSW, Australia 2002-2013

Online Resource 1 Australian Classification of Health Interventions (ACHI) procedure codes

Type of surgery	ACHI Block	ACHI Codes	Description
Breast conserving surgery	1744	30347-00, 31500-00	Excision of lesion of breast
		30342-00	Local excision of lesion of breast
		30346-00	Local excision of lesion of breast with frozen section biopsy
	1745	30342-01	Segmental resection of breast
		30346-01	Segmental resection of breast with frozen section biopsy
	1746	30350-00	Partial mastectomy
		30350-01	Partial mastectomy with frozen section biopsy
Re-excision	1744	30348-00, 31515-00	Re-excision of lesion of breast
Mastectomy	1747	30356-03	Subcutaneous mastectomy with frozen section biopsy, bilateral
		30356-01	Subcutaneous mastectomy with frozen section biopsy, unilateral
		30356-02, 30354-01, 31524-01	Subcutaneous mastectomy, bilateral
		30356-00, 30354-00, 31524-00	Subcutaneous mastectomy, unilateral
	1748	30338-03	Simple mastectomy with frozen section biopsy, bilateral
		30338-01	Simple mastectomy with frozen section biopsy, unilateral
		30338-02, 30351-01, 31518-01	Simple mastectomy, bilateral
		30338-00, 30351-00, 31518-00	Simple mastectomy, unilateral
	1749	30353-03	Extended simple mastectomy with frozen section biopsy, bilateral
		30353-01	Extended simple mastectomy with frozen section biopsy, unilateral
		30353-02	Extended simple mastectomy, bilateral
		30353-00	Extended simple mastectomy, unilateral
	1750	30359-03	Modified radical mastectomy with frozen section biopsy, bilateral
		30359-01	Modified radical mastectomy with frozen section biopsy, unilateral
		30359-02	Modified radical mastectomy, bilateral
		30359-00	Modified radical mastectomy, unilateral
	1751	30359-07	Radical mastectomy with frozen section biopsy, bilateral
		30359-05	Radical mastectomy with frozen section biopsy, unilateral
		30359-06	Radical mastectomy, bilateral
		30359-04	Radical mastectomy, unilateral

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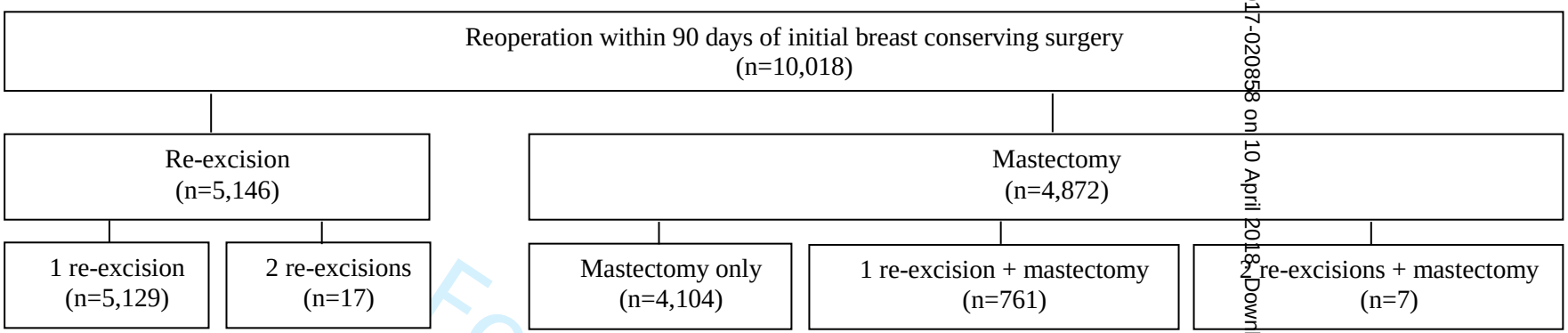
Online Resource 2 Distribution of hospitals and patients by hospital type, surgical volume and hospital location

	Distribution of hospitals		Distribution of patients	
	Metropolitan	Non-metropolitan	Metropolitan	Non-metropolitan
Variable	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Hospital type	p=0.003[a]		p<0.001[a]	
Public	35 (42.2)	51 (65.4)	11,402 (42.9)	4,114 (52.1)
Private	48 (57.8)	27 (34.6)	15,157 (57.1)	3,785 (47.9)
BCS surgical volume[b]	p<0.001[a]		p<0.001[a]	
<1	20 (24.1)	33 (42.3)	78 (0.2)	98 (1.2)
1-4	6 (7.2)	15 (19.2)	128 (0.5)	397 (5.0)
5-14	15 (18.1)	12 (15.4)	1,232 (4.6)	1,365 (17.3)
15-49	24 (28.9)	17 (21.8)	6,844 (25.8)	5,380 (68.1)
50-99	10 (12.1)	1 (1.3)	6,782 (25.5)	659 (8.3)
100+	8 (9.6)	0 (0.0)	11,515 (43.4)	0 (0.0)
Total	83 (100.0)	78 (100.0)	26,559 (100.0)	7,899 (100.0)

Abbreviations: BCS, breast conserving surgery.
[a]*p*-values from Pearson's $\chi 2$ test.
[b]Average annual BCS cases per hospital, 2002-2013.



Online Resource 3 **Flow diagram showing the number of women undergoing re-excision and mastectomy within 90 days of initial breast conserving surgery, NSW, Australia, 2002-2013**

Online Resource 4 **Area- and hospital-level variance (σ^2) and the proportional change in variance (%) between baseline and subsequent models, for any reoperation versus no reoperation, and separately, for re-excision or mastectomy versus no reoperation[a]**

		Any reoperation				Reoperation (re-excision)				Reoperation (mastectomy)			
Model	**Variables**	**σ**	**SE of σ**	**p-value**	**PCV**	**σ**	**SE of σ**	**p-value**	**PCV**	**σ**	**SE of σ**	**p-value**	**PCV**
Random intercept for hospital													
Baseline	Age-group	0.174	0.033	0.000		0.194	0.037	0.000		0.208	0.041	0.000	
Model 2	+ Aboriginal status, country of birth	0.176	0.033	0.000	-1.1	0.195	0.038	0.000	-0.5	0.215	0.044	0.000	-3.4
Model 3	+ tumour type, previous cancer, comorbidities	0.179	0.034	0.000	-2.9	0.197	0.039	0.000	-1.5	0.214	0.043	0.000	-2.9
Model 4	+ calendar year	0.177	0.033	0.000	-1.7	0.204	0.040	0.000	-5.2	0.200	0.040	0.000	3.8
Model 5	+ area-level socioeconomic status	0.178	0.033	0.000	-2.3	0.203	0.039	0.000	-4.6	0.196	0.039	0.000	5.8
Model 6	+ hospital type, BCS surgical volume	0.156	0.031	0.000	10.3	0.201	0.040	0.000	-3.6	0.156	0.033	0.000	25.0
Model 7	+ combined residential and hospital location	0.148	0.030	0.000	14.9	0.201	0.041	0.000	-3.6	0.125	0.028	0.000	39.9
Random intercept for SLA													
Baseline	Age-group	0.002	0.002	0.179		0.010	0.004	0.008		0.007	0.003	0.017	
Model 2	+ Aboriginal status, country of birth	0.002	0.001	0.115	0.0	0.010	0.004	0.007	0.0	0.007	0.003	0.014	0.0
Model 3	+ tumour type, previous cancer, comorbidities	0.002	0.001	0.222	0.0	0.010	0.003	0.005	0.0	0.008	0.003	0.011	-14.3
Model 4	+ calendar year	0.002	0.002	0.210	0.0	0.010	0.004	0.007	0.0	0.007	0.003	0.010	0.00
Model 5	+ area-level socioeconomic status	0.002	0.002	0.198	0.0	0.010	0.004	0.013	0.0	0.007	0.003	0.012	0.00
Model 6	+ hospital type, BCS surgical volume	0.003	0.002	0.160	-50.0	0.009	0.004	0.017	10.0	0.004	0.002	0.035	42.9
Model 7	+ combined residential and hospital location	0.003	0.002	0.148	-50.0	0.009	0.004	0.011	10.0	0.002	0.002	0.191	71.4

Abbreviations: SE, standard error; PCV, proportional change in variance; SLA, statistical local area; BCS, breast conserving surgery.
[a] Multilevel, cross-classified binomial (any reoperation) and multinomial (re-excision, mastectomy) logistic regression models.

Online Resource 5. Adjusted odds ratios for any reoperation versus no reoperation, and separately, for re-excision or mastectomy versus no reoperation within 90 days of initial breast conserving surgery, NSW, Australia 2002-2013[a]

Characteristic	Any reoperation OR (95% CI)	Reoperation (re-excision) OR (95% CI)	Reoperation (mastectomy) OR (95% CI)
Age (years)			
<35	1.22 (1.02-1.47)	0.91 (0.71-1.17)	1.60 (1.28-2.01)
35-49	1.41 (1.33-1.49)	1.24 (1.15-1.34)	1.61 (1.48-1.74)
50-64	1.00	1.00	1.00
65-79	0.89 (0.83-0.94)	0.82 (0.76-0.89)	0.96 (0.89-1.04)
80+	0.51 (0.45-0.58)	0.37 (0.30-0.44)	0.69 (0.59-0.80)
Aboriginal status			
Non-Aboriginal	1.00	1.00	1.00
Aboriginal	1.13 (0.88-1.47)	0.87 (0.60-1.25)	1.40 (1.03-1.89)
Country of birth			
Australia/New Zealand	1.00	1.00	1.00
Europe	1.02 (0.95-1.09)	0.99 (0.90-1.09)	1.04 (0.94-1.14)
East Asia	1.22 (1.10-1.35)	1.15 (1.02-1.31)	1.29 (1.13-1.47)
Other	1.01 (0.92-1.10)	1.02 (0.91-1.14)	0.99 (0.88-1.13)
Unknown	0.94 (0.80-1.11)	0.94 (0.76-1.16)	0.95 (0.76-1.18)
Tumour type			
Invasive	1.00	1.00	1.00
Insitu/mixed	1.81 (1.72-1.91)	1.76 (1.64-1.89)	1.86 (1.74-1.99)
Previous breast cancer[b]			
No	1.00	1.00	1.00
Yes	0.55 (0.40-0.78)	0.52 (0.33-0.83)	0.58 (0.38-0.90)
Other previous cancer[b]			
No	1.00	1.00	1.00
Yes	0.85 (0.64-1.13)	0.74 (0.50-1.10)	0.95 (0.67-1.35)
Number of comorbidities[b]			
No comorbidities	1.00	1.00	1.00

Characteristic	Any reoperation OR (95% CI)	Reoperation (re-excision) OR (95% CI)	Reoperation (mastectomy) OR (95% CI)
1 comorbidity	0.91 (0.82-1.01)	0.89 (0.77-1.02)	0.93 (0.82-1.07)
2 comorbidities	1.01 (0.78-1.31)	0.82 (0.57-1.18)	1.17 (0.86-1.60)
3+ comorbidities	0.68 (0.42-1.12)	0.64 (0.31-1.31)	0.69 (0.36-1.33)
Year of BCS			
2002-2005	1.00	1.00	1.00
2006-2009	1.00 (0.94-1.06)	1.22 (1.12-1.32)	0.84 (0.77-0.91)
2010-2013	0.92 (0.86-0.97)	1.21 (1.12-1.31)	0.69 (0.64-0.75)
Index of relative socioeconomic disadvantage[c]			
Quintile 5 (Least disadvantaged)	1.00	1.00	1.00
Quintile 4	1.03 (0.94-1.11)	1.03 (0.92-1.15)	1.01 (0.91-1.12)
Quintile 3	0.97 (0.89-1.07)	0.94 (0.83-1.07)	0.99 (0.89-1.11)
Quintile 2	1.02 (0.91-1.14)	1.02 (0.87-1.19)	1.02 (0.89-1.16)
Quintile 1 (Most disadvantaged)	1.03 (0.93-1.15)	1.07 (0.93-1.23)	0.99 (0.87-1.12)
Hospital type			
Public	1.00	1.00	1.00
Private	1.12 (0.95-1.31)	1.20 (0.99-1.46)	1.09 (0.92-1.28)
BCS surgical volume[d]			
<15	1.00	1.00	1.00
15-49	0.78 (0.64-0.96)	0.88 (0.69-1.12)	0.71 (0.59-0.85)
50+	0.85 (0.66-1.09)	0.93 (0.69-1.24)	0.73 (0.57-0.93)
Residential and hospital location			
Metropolitan x metropolitan	1.00	1.00	1.00
Metropolitan x non-metropolitan	1.21 (0.85-1.73)	1.25 (0.79-1.99)	1.14 (0.79-1.66)
Non-metropolitan x metropolitan	0.98 (0.88-1.09)	0.93 (0.81-1.06)	1.04 (0.91-1.20)
Non-metropolitan x non-metropolitan	1.24 (1.02-1.52)	0.96 (0.75-1.22)	1.45 (1.20-1.76)

Abbreviations: OR, odds ratio; CI, confidence interval; BCS, breast conserving surgery.

[a] ORs obtained from multilevel, cross-classified binomial (any reoperation) and multinomial (re-excision, mastectomy) logistic regression models, adjusted for patient-level factors, calendar year, area-level contextual factors, and health system-level factors.

[b] Recorded on or within 12 months prior to initial BCS.

[c] Index of relative socioeconomic disadvantage for statistical local area of residence.

[d] Average annual number of BCS cases per hospital, 2002-2013.

Online Resource 6 **Adjusted odds ratios for mastectomy versus re-excision in women undergoing re-operation within 90 days of initial breast conserving surgery, NSW, Australia 2002-2013**[a]

Characteristic	Mastectomy (versus re-excision) OR (95% CI)
Age (years)	
<35	1.78 (1.31-2.42)
35-49	1.29 (1.17-1.43)
50-64	1.00
65-79	1.17 (1.05-1.29)
80+	1.87 (1.47-2.37)
Aboriginal status	
Non-Aboriginal	1.00
Aboriginal	1.60 (1.03-2.49)
Country of birth	
Australia/New Zealand	1.00
Europe	1.03 (0.91-1.17)
East Asia	1.10 (0.94-1.28)
Other	0.99 (0.84-1.16)
Unknown	1.02 (0.77-1.33)
Tumour type	
Invasive	1.00
Insitu/mixed	1.06 (0.98-1.16)
Previous breast cancer[b]	
No	1.00
Yes	1.12 (0.61-2.08)
Other previous cancer[b]	
No	1.00
Yes	1.38 (0.84-2.26)
Number of comorbidities[b]	
No comorbidities	1.00

Characteristic	Mastectomy (versus re-excision) OR (95% CI)
1 comorbidity	1.06 (0.88-1.27)
2 comorbidities	1.52 (0.96-2.40)
3+ comorbidities	1.19 (0.47-3.02)
Year of BCS	
2002-2005	1.00
2006-2009	0.69 (0.63-0.77)
2010-2013	0.57 (0.51-0.63)
Index of relative socioeconomic disadvantage[c]	
Quintile 5 (Least disadvantaged)	1.00
Quintile 4	1.00 (0.88-1.14)
Quintile 3	1.06 (0.92-1.23)
Quintile 2	1.01 (0.85-1.20)
Quintile 1 (Most disadvantaged)	0.94 (0.80-1.10)
Hospital type	
Public	1.00
Private	0.90 (0.77-1.07)
BCS surgical volume[d]	
<15	1.00
15-49	0.81 (0.67-0.98)
50+	0.79 (0.63-0.99)
Residential and hospital location	
Metropolitan x metropolitan	1.00
Metropolitan x non-metropolitan	0.88 (0.60-1.29)
Non-metropolitan x metropolitan	1.15 (0.97-1.36)
Non-metropolitan x non-metropolitan	1.49 (1.23-1.80)

Abbreviations: OR, odds ratio; CI, confidence interval; BCS, breast conserving surgery.
[a] ORs obtained from multilevel, cross-classified binomial (mastectomy versus re-excision) logistic regression models in women undergoing reoperation (n=10,018), adjusted for patient-level factors, calendar year, area-level contextual factors, and health system-level factors.
[b] Recorded on or within 12 months prior to initial BCS.
[c] Index of relative socioeconomic disadvantage for statistical local area of residence.
[d] Average annual number of BCS cases per hospital, 2002-2013.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1, 3
Objectives	3	State specific objectives, including any prespecified hypotheses	1, 3
Methods			
Study design	4	Present key elements of study design early in the paper	1, 3, 4-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-7
Bias	9	Describe any efforts to address potential sources of bias	6-7, 11-12
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4
		(b) Give reasons for non-participation at each stage	4
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	8, Table 1
		(c) Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	Report numbers of outcome events or summary measures over time	8, Table 2, Online Resource 3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2
		(*b*) Report category boundaries when continuous variables were categorized	5-6, all tables and figures
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	6, Table 2
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Fig 2-3, Online Resources
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Reoperation after breast conserving surgery for cancer in Australia: statewide cohort study of linked hospital data

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Title: Reoperation after breast conserving surgery for cancer in Australia: statewide cohort study of linked hospital data

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ABSTRACT

Objectives: To investigate between-hospital variation in the probability of reoperation within 90 days of initial breast conserving surgery (BCS), and the contribution of health system-level and other factors.

Design: Population-based, retrospective cohort study.

Setting: New South Wales (NSW), Australia.

Participants: Linked administrative hospitalisation data were used to define a cohort of adult women undergoing initial BCS for breast cancer in NSW between 1 July 2002 and 31 December 2013.

Primary outcome measures: Multilevel, cross-classified models with patients clustered within hospitals and residential areas were used to examine factors associated with any re-operation, and either re-excision or mastectomy, within 90 days.

Results: Of 34,458 women undergoing BCS, 29.1% underwent reoperation within 90 days, half of which were mastectomies. Overall, the probability of reoperation decreased slightly over time. However, there were divergent patterns by reoperation type; the probability of re-excision increased alongside a concomitant decrease in the probability of mastectomy. Significant between-hospital variation was observed. Non-metropolitan location and surgery at low-volume hospitals were associated with a higher overall probability of reoperation, and of mastectomy specifically, after accounting for patient-level factors, calendar year and area-level socioeconomic status. The magnitude of association with geographic location and surgical volume decreased over time.

Conclusions: Reoperation rates within 90 days of BCS varied significantly between hospitals. For women undergoing mastectomy after BCS, this represents a dramatic change in clinical course. Multilevel modelling suggests unwarranted clinical variation may be an issue, likely due to disparities in access to multidisciplinary breast cancer care and preoperative diagnostic

procedures. However, the observed reduction in disparities over time is encouraging and indicates that guidelines and policy initiatives have the potential to improve regional breast cancer care.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The primary strength of this study is the use of best-practice multi-level modelling to investigate health-system level factors associated with reoperation after breast conserving surgery.
- One limitation is the lack of detailed information on tumour characteristics known to contribute to margin status.
- Another limitation is the inability to incorporate patient or surgeon perspectives which may have influenced surgical decisions.

INTRODUCTION

Clinical practice guidelines recommend that, where appropriate, women with early-stage breast cancer be offered either breast conserving surgery (BCS) with radiotherapy, or mastectomy.[1 2] Survival following BCS and radiotherapy is comparable to that following mastectomy. [3] However, BCS is associated with fewer post-operative complications [4] and improved quality of life. [5] In Australia, between 60-80% of women with early-stage breast cancer choose BCS,[6-8] with similar figures reported in the United States.[9]

However, a number of women who undergo BCS require reoperation, either re-excision or completion mastectomy.[10 11] This causes pain, suffering and anxiety, and may result in poorer cosmetic outcomes[12] and higher rates of recurrence due to delays in commencing adjuvant therapy.[13] The financial costs of reoperation are also considerable.[14] Population-based studies in the United States[10] and England[11] estimate the rate of reoperation ranges between 20-30%, though recent data suggest a downtrend in rates following the dissemination of clinical guidelines regarding surgical margins.[15] Previous Australian data are limited; a rate of 30% was estimated based on linked registry from Western Australia, 1998-2000.[8]

Factors associated with reoperation can be broadly divided into patient-level sociodemographic and clinical factors, together with health system-level factors.[16] Comprehensive investigation into health-system factors, which are potentially modifiable, is lacking, with few large population-based studies conducted,[8 10 11 17] only one of which[10] used best-practice multilevel modelling techniques to capture health system-level variation. If confirmed, variation in reoperation rates related to health system, rather than patient-level factors, has important policy and practice implications. We present multilevel, cross-classified models examining patient-level, area-level contextual and health system-level factors associated with reoperation following BCS for breast cancer in a statewide, population-based cohort of women from New South Wales (NSW), Australia, 2002-2013.

METHODS

Data sources and study population

The NSW Admitted Patient Data Collection (APDC) records inpatient separations from all hospitals in NSW. Patient demographics, together with principal and secondary diagnoses and procedures are recorded for each separation. Diagnoses are coded according to the International Statistical Classification of Diseases and Related Problems, 10th Revision, Australian Modification, (ICD-10-AM) and procedures according to the Australian Classification of Health Interventions (ACHI). The NSW Registry of Births, Deaths and Marriages (RBDM) records all deaths registered in NSW. An extract of the NSW APDC containing records between 1 July 2001 and 31 March 2014 was linked with the NSW RBDM by the NSW Centre for Health Record Linkage (http://www.cherel.org.au/) using an established probabilistic linkage method. Ethical approval was obtained from the NSW Population and Health Services Research Ethics Committee and the NSW Aboriginal Health and Medical Research Council Ethics Committee.

These data were used to define a cohort of adult (≥16 years) women with a diagnosis of invasive (ICD-10-AM C50) or insitu (ICD-10-AM D05) breast cancer who underwent initial BCS in NSW hospitals between 1 July 2001 and 31 March 2014, based on either principal or secondary diagnosis and procedure codes (n=39,255). We excluded women whose initial BCS occurred prior to 1 July 2002 (n=3,070); this ensured a lookback period of at least 12 months in which to assess record of previous breast or other cancer, and comorbidities. Similarly, we excluded women with less than 90 days follow-up after their initial BCS (n=896), either because it occurred after 31 December 2013, or they died within 90 days. We also excluded women who were not permanent residents of NSW (n=831). This left a final analytical cohort of n=34,458 women (Figure 1).

BCS was defined by ACHI procedure codes for excision of lesion of breast (includes excisional biopsy), local excision of lesion of breast, segmental resection of breast, and partial mastectomy (see Online Resource 1 for codes). Breast reoperation was defined by procedure codes for re-excision or mastectomy within 90 days of initial BCS. A period of 90 days was applied to avoid including reoperations for local recurrence. Open (incisional) biopsy (30344-00, 31500-01) was not considered BCS. In women undergoing both re-excision and mastectomy following BCS, mastectomy was taken as the definitive procedure.

Explanatory variables

Patient-level sociodemographic variables at initial BCS included: age-group; Australian Aboriginal or Torres Strait Islander status (hereafter referred to as 'Aboriginal'); and, country of birth. Patient-level clinical variables included: invasive or insitu tumour type; previous breast cancer recorded up to 12 months prior to initial BCS; and, other previous cancer and comorbidities (defined as per Charlson[18]), recorded either at admission for initial BCS or up to 12 months prior. Previous breast cancer was assigned only where it could be determined that the record was not related to the diagnosis of, or neoadjuvant treatment for, the current breast tumour. Calendar year of initial BCS was also included.

Patient-level socioeconomic status is not recorded on the APDC; however, the Index of Relative Socioeconomic Disadvantage (IRSD, quintiles) was included as an area-level contextual variable, based on statistical local area of residence (SLA) defined using boundaries from the 2006 Australian Census.[19] SLAs are one of the smallest geographic units available in the Australian Standard Geographical Classification, with 199 across the status of NSW (average population 32,859, range 346-133,837).[20]

Health system-level variables at initial BCS included hospital identifier, public or private hospital type and BCS surgical volume (<15, 15-49, 50+), based on the average annual

number of BCS cases. Categorisation of BCS surgical volume was informed by visual inspection of its distribution [not shown]. Geographic remoteness (metropolitan, non-metropolitan) was defined according to the Accessibility/Remoteness Index of Australia,[20] and categorised as the combination of residential and hospital location, in order to capture differences in access to specialist, multidisciplinary inpatient breast cancer care, as well as outpatient services, such as mammographic screening and preoperative diagnosis. While the majority (95.3%) of women living in metropolitan areas underwent initial BCS in metropolitan hospitals, only 72.1% of women living in non-metropolitan areas were treated in non-metropolitan hospitals [data not shown elsewhere]. Note, we did not consider hospital transfers between the hospital in which the initial BCS was conducted and that of the reoperation; factors related to the initial BCS were our primary interest.

Statistical analysis

Multilevel, cross-classified logistic regression models were used to examine the probability of reoperation versus no reoperation (binomial) and re-excision or mastectomy versus no-reoperation (multinomial) within 90 days of initial BCS; supplementary binomial modelling examining the probability of mastectomy versus re-excision was also performed. Individuals were treated as the unit of analysis, and were clustered according to both the hospital in which their initial BCS was performed and their SLA of residence, using cross-classified random intercept parameters. Variation in the probability of reoperation between hospitals and between SLAs was quantified using the variance of the random intercept parameters.[21]

Baseline models included the random intercepts for hospital and SLA, and age-group at initial BCS, with subsequent models sequentially adding other patient-level sociodemographic and clinical variables, calendar year, area-level contextual and health system-level variables. Adjusted odds ratios (ORs) were obtained by exponentiating the regression parameters.

Population-averaged, predicted probabilities of reoperation (expressed as a percentage) were also estimated from the fitted model. We examined whether the association between health system-level factors and the probability of reoperation varied over time by separately including interaction terms between geographic location, BCS surgical volume and calendar (as a continuous variable) year of initial BCS in the corresponding main effect model.

All data preparation was performed in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), and all modelling in MLwiN version 2.35 (Browne et al., Centre for Multilevel Modelling, University of Bristol). For all statistics, *p*-values were two-tailed, and alpha was set at 0.05.Models were fitted using Markov Chain Monte Carlo (MCMC) estimation with inference based on 20,000 samples following a burn-in of 5,000. Trajectories of stored parameter estimates were visually checked for irregular distributions and convergence to a unimodal distribution.

RESULTS

Cohort characteristics

Between 1 July 2002 and 31 December 2013, 34,458 women with breast cancer underwent initial BCS in 161 NSW hospitals. The median age at initial BCS was 59 years (interquartile range 50-67 years). The majority (68.9%) of women were born in Australia/New Zealand, and 0.9% identified as Aboriginal (Table 1). Most women had invasive tumours, with 26.6% having insitu tumours, or tumours with an insitu component; of these tumours n=6,377 (69.6%) were DCIS [data not shown elsewhere]. A small proportion (0.7%) of women had previous breast cancer, 0.8% had another cancer, and 8.0% had comorbidities recorded in hospital admissions data at or within 12 months of initial BCS. Most women (69.5%) both resided and underwent initial BCS in metropolitan areas. Over half (55.0%) attended private hospitals and a similar figure attended high-volume hospitals (≥50 BCS cases per year). Women undergoing BCS in non-metropolitan hospitals were significantly less likely to have attended a private or high-volume hospital (see Online Resource 2 for cross-tabulation).

As shown in Table 2, 10,018 (29.1%) of women underwent at least one reoperation within 90 days of initial BCS, either re-excision (n=5,146, 14.9%) or mastectomy (n=4,872, 14.1%). Of women undergoing mastectomy, 15.8% had also undergone re-excision (see Online Resource 3 for flow diagram). The proportion of women undergoing reoperation decreased slightly over time, from 30.1% to 27.8%. Divergent patterns were observed by reoperation type; the proportion of women undergoing re-excision increased over time, from 12.8% in 2002-2005 to 15.9% in 2010-2013, whereas the proportion of women undergoing completion mastectomy decreased from 17.2% to 11.9%.

Multilevel modelling

The population-averaged predicted probability of reoperation was 28.2%, with estimates of 14.6% and 13.4% for re-excision and mastectomy respectively (Table 2). Significant variation was observed between hospitals in the overall probability of reoperation, as well as for re-excision and mastectomy, in both baseline and adjusted models (see Online Resource 4 for variance). Significant variation was also observed between residential SLAs in the probability of re-excision and mastectomy, though this was notably smaller than the variation seen between hospitals.

A clear pattern emerged for some explanatory factors (Table 2; Online Resources 5-6). The probability of reoperation, whether by re-excision or mastectomy, was consistently higher among women of East Asian origin and those with insitu tumours, and was consistently lower for women with a previous breast cancer. The probability of reoperation was consistently higher among younger women compared with women aged 50-64 (the target age group for mammographic screening in Australia) and lower among older women; women undergoing reoperation in these age groups were significantly more likely to undergo mastectomy than re-excision. There was no association between reoperation and other previous cancers, the number of comorbidities, area-level socioeconomic status, or public or private hospital type.

For other factors, there were notable differences in the pattern of reoperation by re-excision or mastectomy (Table 2; Figure 2; Online Resources 5-6). As per the descriptive analyses, there was a decrease in the overall probability of reoperation over time, however, divergent patterns were observed; the probability of re-excision increased alongside a concomitant decrease in that for mastectomy. Women attending lower-volume hospitals had a higher overall probability of reoperation compared with those attending higher-volume (≥15 BCS cases per year) hospitals. Women living in non-metropolitan areas and who attended non-metropolitan hospitals had a higher overall probability of reoperation than those living in metropolitan areas and who attended metropolitan hospitals. Both these associations were seen for

mastectomy, but not for re-excision. Significant interactions were observed between the effect of year of initial BCS and each of geographic location ($p<0.001$) and volume ($p=0.008$) on the probability of mastectomy, with the magnitude of the differences reducing over time (Figure 3). There was no difference in the overall probability of reoperation by indigenous status, although Aboriginal women had a higher probability of mastectomy than non-Aboriginal women, based on small numbers.

DISCUSSION

In this statewide, population-based study of women undergoing initial BCS for breast cancer in Australia during 2002-2013, 29.1% underwent reoperation within 90 days, almost half undergoing mastectomy. Significant between-hospital variation was observed. Overall, the probability of reoperation decreased slightly over time. However, there were divergent patterns by reoperation type; the probability of re-excision increased alongside a concomitant decrease in the probability of mastectomy. Women living in non-metropolitan areas and who attended non-metropolitan hospitals, as well as those attending low-volume hospitals, had a higher probability of reoperation, particularly mastectomy, even after adjusting for patient- and area-level contextual factors. The magnitude of association with geographic location and volume decreased over time.

This is the first study to have used multilevel modelling to thoroughly investigate the role of health system-level, area-level contextual and patient-level factors in reoperation following BCS. It is also the first to have applied multilevel multinomial modelling to separately examine factors associated with re-excision and mastectomy; this is important, as some associations were obscured when examined for all reoperations combined, in a demonstration of Simpson's paradox.[22]

This is one of few published population-based studies. NSW hospitalisation data have been demonstrated to have high sensitivity and specificity in identifying breast cancer patients when validated against cancer registry data,[23] and to provide unbiased estimates of BCS.[24] However, the potential for miscoding within administrative datasets is acknowledged. Further, due to inherent characteristics of ICD-10-AM diagnostic codes, it is not possible to distinguish excisional biopsies performed for diagnostic purposes from those performed with the intention of complete excision.[8] We were unable to account for laterality. However, the availability in ICD-10-AM of a diagnostic code specific for re-excision and the low likelihood

of contralateral mastectomy within 90 days of BCS means that any misclassification of reoperation due to absence of data on laterality would be minimal. We could not consider margin status, nor fully account for stage, histology and other tumour characteristics known to contribute to margin status. However, it is unlikely that variation based on these factors would have accounted for the hospital variation we observed. Finally, we could not incorporate patient or surgeon perspectives; the complexities of decision-making in the surgical treatment of breast cancer cannot be adequately assessed using administrative data.[8]

Our observed overall reoperation rate is similar to that for contemporaneous, population-based cohorts in the United States (New York, 2002-2013; 31%)[10] and the Netherlands (Rotterdam, 2006-2007; 29%)[25] but higher than that from the United Kingdom (England, 2005-2008; 20%).[11] Lower rates were reported from Spain (Catalonia, 2005-2011; 12%)[26] and Ireland (2002-2008; 17%)[17] but these studies did not include DCIS.

Variability in reoperation rates can be partly explained by differences in approach to surgical margins. Reoperation primarily occurs due to positive or negative close margins.[27] Historically, there has been lack of consensus on what constitutes an adequate negative margin,[28 29] though in the context of multimodality breast cancer treatment, wider margins are no longer superior in terms of local recurrence.[15] Consensus guidelines were recently published recommending 'no ink on tumour' as an adequate surgical margin for patients with early-stage invasive breast cancer undergoing BCS with radiotherapy (2014)[30] and 2mm for DCIS (2016).[31] This fundamental shift in approach is reflected in our observation of changing proportions of women undergoing re-excision and mastectomy over time, also noted in the New York cohort,[10] and in recent analyses of United States Surveillance, Epidemiology and End Results registry data.[15]

Between-hospital variation in reoperation rates has not been previously demonstrated using multilevel analyses. Variability in reoperation rates between surgeons was observed in the New York cohort,[10] as well as in a multi-site cohort of United States' breast cancer patients, though this study was not population-based.[32] Surgical volume, an accepted surrogate for specialisation, is one possible explanation.[10 17 25 27 32 33] Specialist breast cancer surgeons may be more proficient at obtaining negative margins, and less likely to re-excise close margins.[16] Patient selection and appropriateness of BCS as the initial treatment choice is also a factor. Anecdotal evidence suggests that treatment decisions made in high-volume hospitals are often made by multidisciplinary teams (MDTs), and differ from those made by clinicians working in isolation.[34]

Differences in the probability of reoperation, particularly mastectomy, between women living and undergoing treatment in metropolitan versus non-metropolitan areas potentially reflects differential access to specialist, multidisciplinary breast cancer care. A 2006 survey of Australian breast cancer surgeons showed, for example, that participation in MDTs is higher for surgeons in metropolitan than non-metropolitan areas.[35] Differential access to specialised radiological services able to perform localisation of impalpable lesions and intraoperative assessment to confirm complete excision may also be a valid consideration, as is access to preoperative diagnostic services.[8] Women in remote areas of Australia are less likely to have undergone preoperative diagnosis by fine-needle aspiration or core biopsy, and instead, more likely to have undergone surgical biopsy[36]; this may be exacerbated by lower rates of mammographic screening and referral for preoperative diagnosis.[37] Increased risk of reoperation could be expected therefore, as BCS may have been performed for diagnostic purposes rather than with the intention of complete excision.[8] This was evidenced in US surgical[32] and Medicare cohort data[33] where lack of preoperative diagnosis was associated with higher rates of reoperation.

Health system-level factors were found to be significant independent of patient-level factors, such as younger age,[8 10 11 17 27 38] and insitu tumour type.[10 11 38] Positive margins are more frequently observed in younger women, as smaller volumes of breast tissue are resected and tumours tend to have adverse histologic features.[39 40] In addition, preoperative diagnosis in younger women may be complicated by greater breast density and lower mammographic sensitivity.[40] Comparatively smaller breast size and greater breast density[41] may similarly account for the high probability of reoperation seen in Asian women.[38] Most (70%) insitu tumours in our cohort were DCIS. The margins of DCIS are less well defined than for invasive tumours, and extension into the breast tissue can be difficult to determine.[42] Hence, DCIS is more often associated with positive margins.[43 44] The higher probability of mastectomy seen among Aboriginal women should be interpreted cautiously due to small numbers, but nevertheless suggests they may be a high-risk group, independent of their place of residence. Aboriginal women in Australia have lower rates of screening participation,[37 45] disparate access to BCS,[7] and lower survival after breast cancer surgery.[45] Interestingly, we did not observe an association with area-level socioeconomic status, which has been related to differential access to BCS[7 46] and survival,[47] but not to differences in rates of screening.[37]

In summary, in a population-based cohort of Australian women, 29.1% underwent reoperation within 90 days of BCS, almost half undergoing mastectomy. For these women, this represents a dramatic change in clinical course. We used robust statistical methodology to show between-hospital variation in reoperation rates, and an association with health system-level factors, after considering patient- and area-level contextual factors.

The association of low BCS surgical volume and non-metropolitan location with mastectomy after BCS highlights the potential role of access to multidisciplinary, specialist breast cancer care in reducing unwarranted clinical variation. Other considerations should include: improving access to high-quality preoperative diagnostic imaging and biopsy, methods to

localise non-palpable tumours, intraoperative margin assessment, as well as surgeon education in oncoplastic techniques and compliance with margin guidelines. This is not unique to the Australian setting; a consensus conference held among the American Society of Breast Cancer Surgeons in 2015 advocated several such evidence-based recommendations to reduce variability in reoperation rates.[48] Disparities in the reoperation rate between metropolitan and non-metropolitan areas, and between low- and high-volume hospitals, appear to have reduced. This is encouraging, and suggests that policy initiatives to improve regional breast cancer care in NSW over the past decade may have had some success.[49 50]

AUTHOR CONTRIBUTIONS

All authors (MvL, MF, CV, PC, SL, EK, LJ, AS) made substantial contributions to the study concept and design. MvL had full access to the study data. MvL, CV, MF, and SL were responsible for developing the analytical protocol, and MvL and MF for executing the statistical analyses. All authors (MvL, MF, CV, PC, SL, EK, LJ, AS) made substantial contributions to the interpretation of the data. MvL, MF, and CV drafted the manuscript; all authors (MvL, MF, CV, PC, SL, EK, LJ, AS) revised it critically for important intellectual content. All authors (MvL, MF, CV, PC, SL, EK, LJ, AS) have approved the final version of the manuscript.

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COMPETING INTERESTS

The authors declare that they have no conflict of interest.

DATA SHARING

No additional data are available.

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TABLES

Table 1 **Patient-level, area-level contextual, and health system-level characteristics of women undergoing breast conserving surgery 2002-2013, NSW, Australia**

Variable	N (%)
Total cohort	34,458 (100.0)
Age (years)	
<35	579 (1.7)
35-49	7,308 (21.2)
50-64	15,209 (44.1)
65-79	9,309 (27.0)
80+	2,053 (6.0)
Aboriginal status	
Non-Aboriginal	34,161 (99.1)
Aboriginal	297 (0.9)
Country of birth	
Australia/New Zealand	23,746 (68.9)
Europe	4,863 (14.1)
East Asia	2,217 (6.4)
Other	2,808 (8.2)
Unknown	824 (2.4)
Tumour type	
Invasive	25,291 (73.4)
Insitu/insitu component	9,167 (26.6)
Previous breast cancer[a]	
No	34,211 (99.3)
Yes	247 (0.7)
Other previous cancer[a]	
No	34,169 (99.2)
Yes	289 (0.8)
Number of comorbidities[a]	
No comorbidities	31,689 (92.0)
1 comorbidity	2,303 (6.7)
2 comorbidities	348 (1.0)
3+ comorbidities	118 (0.3)
Year of initial BCS	
2002-2005	9,868 (28.6)
2006-2009	11,662 (33.8)
2010-2013	12,928 (37.5)
Index of relative socioeconomic disadvantage[b]	
Quintile 5 (Least disadvantaged)	12,319 (35.8)
Quintile 4	7,116 (20.7)
Quintile 3	6,860 (19.9)
Quintile 2	4,104 (11.9)
Quintile 1 (Most disadvantaged)	4,059 (11.8)

Variable	N (%)
Hospital type	
Public	15,516 (45.0)
Private	18,942 (55.0)
BCS surgical volume[c]	
<15	3,278 (9.5)
15-49	12,224 (35.5)
50+	18,956 (55.0)
Residential and hospital location	
Metropolitan x metropolitan	23,957 (69.5)
Metropolitan x non-metropolitan	2,602 (7.6)
Non-metropolitan x metropolitan	1,180 (3.4)
Non-metropolitan x non-metropolitan	6,719 (19.5)

Abbreviations: BCS, breast conserving surgery.
[a] Recorded on or within 12 months prior to initial BCS.
[b] Index of relative socioeconomic disadvantage for statistical local area of residence.
[c] Average annual number of BCS cases per hospital, 2002-2013.

Table 2 **Adjusted and unadjusted probabilities of any reoperation, and separately, of re-excision or mastectomy within 90 days of initial breast conserving surgery, NSW, Australia 2002-2013.[a]**

	Any reoperation		Reoperation (re-excision)		Reoperation (mastectomy)	
Variable	N	Adjusted % (unadjusted %)[a]	N	Adjusted % (unadjusted %)[a]	N	Adjusted % (unadjusted %)[a]
Total cohort	10,018	28.5 (29.1)	5,146	14.6 (14.9)	4,872	13.4 (14.1)
Age (years)						
<35	186	32.6 (32.1)	79	13.3 (13.6)	107	18.8 (18.5)
35-49	2,645	35.6 (36.2)	1,290	17.1 (17.7)	1,355	18.0 (18.5)
50-64	4,410	28.4 (29.0)	2,418	15.5 (15.9)	1,992	12.5 (13.1)
65-79	2,429	26.1 (26.1)	1,225	13.2 (13.2)	1,204	12.5 (12.9)
80+	348	17.2 (17.0)	134	6.7 (6.5)	214	10.1 (10.4)
Aboriginal status						
Non-Aboriginal	9,925	28.5 (29.1)	5,111	14.4 (15.0)	4,814	13.3 (14.1)
Aboriginal	93	31.2 (31.3)	35	12.1 (11.8)	58	18.1 (19.5)
Country of birth						
Australia/New Zealand	6,864	28.0 (28.9)	3,478	14.6 (14.7)	3,386	13.4 (14.3)
Europe	1,335	28.4 (27.5)	692	14.4 (14.2)	643	13.9 (13.2)
East Asia	776	32.1 (35.0)	406	15.8 (18.3)	370	16.3 (16.7)
Other	800	28.2 (28.5)	444	14.8 (15.8)	356	13.3 (12.7)
Unknown	243	26.8 (29.5)	126	14.0 (15.3)	117	13.0 (14.2)
Tumour type						
Invasive	6,557	25.2 (25.9)	3,404	13.2 (13.5)	3,153	12.1 (12.5)
Insitu/mixed	3,461	37.6 (37.8)	1,742	19.1 (19.0)	1,719	18.5 (18.8)
Previous breast cancer[b]						
No	9,973	28.6 (29.2)	5,125	14.5 (15.0)	4,848	13.5 (14.2)
Yes	45	18.5 (18.2)	21	8.9 (8.5)	24	9.2 (9.7)
Previous other cancer[b]						
No	9,951	28.4 (29.1)	5,117	14.4 (15.0)	4,834	13.3 (14.2)
Yes	67	25.5 (23.2)	29	11.4 (10.0)	38	13.4 (13.2)

Variable	Any reoperation N	Any reoperation Adjusted % (unadjusted %)[a]	Reoperation (re-excision) N	Reoperation (re-excision) Adjusted % (unadjusted %)[a]	Reoperation (mastectomy) N	Reoperation (mastectomy) Adjusted % (unadjusted %)[a]
Number of comorbidities[b]						
No comorbidities	9,357	28.4 (29.5)	4,836	15.0 (15.3)	4,521	13.8 (14.3)
1 comorbidity	557	26.7 (24.2)	268	13.6 (11.6)	289	13.2 (12.6)
2 comorbidities	84	28.7 (24.1)	33	12.5 (9.5)	51	16.2 (14.7)
3+ comorbidities	20	22.0 (17.0)	9	11.1 (7.6)	11	10.9 (9.3)
Year of initial BCS						
2002-2005	2,974	29.4 (30.1)	1,282	12.3 (13.0)	1,692	16.0 (17.2)
2006-2009	3,445	29.4 (29.5)	1,805	15.0 (15.5)	1,640	13.4 (14.1)
2010-2013	3,599	27.7 (27.8)	2,059	15.3 (15.9)	1,540	11.4 (11.9)
Index of relative socioeconomic disadvantage[c]						
Quintile 5 (Least disadvantaged)	3,656	28.7 (29.7)	1,955	14.4 (15.9)	1,701	13.5 (13.8)
Quintile 4	2,065	29.2 (29.0)	1,086	14.8 (15.3)	979	13.5 (13.8)
Quintile 3	1,957	28.2 (28.5)	942	13.7 (13.7)	1,015	13.5 (14.8)
Quintile 2	1,189	29.1 (29.0)	560	14.6 (13.7)	629	13.6 (15.3)
Quintile 1 (Most disadvantaged)	1,151	29.4 (28.4)	603	15.3 (14.9)	548	13.2 (13.5)
BCS surgical volume[d]						
<15	1,109	32.1 (33.8)	475	14.8 (14.5)	634	16.8 (19.3)
15-49	3,373	27.3 (27.6)	1,652	14.0 (13.5)	1,721	12.9 (14.1)
50+	5,536	28.7 (29.2)	3,019	14.7 (15.9)	2,517	13.1 (13.3)
Residential and hospital location						
Metropolitan x metropolitan	6,859	27.7 (28.6)	3,705	14.7 (15.5)	3,154	12.6 (13.2)
Metropolitan x non-metropolitan	425	31.6 (36.0)	236	17.6 (20.0)	189	13.7 (16.0)
Non-metropolitan x metropolitan	656	27.4 (25.2)	329	13.7 (12.6)	327	13.2 (12.6)
Non-metropolitan x non-metropolitan	2,078	32.2 (30.9)	876	13.4 (13.0)	1,202	17.4 (17.9)

Abbreviations: BCS, breast conserving surgery.

[a] Adjusted % (predicted probability) obtained from multilevel, cross-classified binomial (any reoperation) and multinomial (re-excision, mastectomy) logistic regression models, adjusted for patient-level factors, calendar year, area-level contextual factors, and health system-level factors.

[b] Recorded on or within 12 months prior to initial BCS.

[c] Index of relative socioeconomic disadvantage for statistical local area of residence.

[d] Average annual number of BCS cases per hospital, 2002-2013.

FIGURE LEGENDS

Figure 1 **Flow diagram showing study inclusion and exclusion criteria**

Figure 2 **Adjusted odds ratios for any reoperation versus no reoperation, and separately, for re-excision or mastectomy versus no reoperation within 90 days of initial breast conserving surgery, NSW, Australia, 2002-2013.** Shows ORs for calendar year and health system-level factors fully adjusted for patient-level and area-level contextual factors based on multilevel, cross-classified binomial (any reoperation) and multinomial (re-excision, mastectomy) logistic regression models.

Figure 3 **Population-averaged predicted probabilities of any reoperation, and separately, of re-excision or mastectomy, within 90 days of initial breast conserving surgery, by calendar year and location, NSW, Australia, 2002-2013.** Predicted probabilities obtained from fully adjusted multilevel, cross-classified binomial (any reoperation) and multinomial (re-excision, mastectomy) logistic regression models containing interaction terms between discrete calendar years geographic location. For illustrative purposes, graph restricted to concordant metropolitan or non-metropolitan residential and hospital location.

ONLINE RESOURCES

Online Resource 1	Australian Classification of Health Interventions (ACHI) procedure codes
Online Resource 2	Distribution of hospitals and patients by hospital type, surgical volume and hospital location
Online Resource 3	Flow diagram showing the number of women undergoing re-excision and mastectomy within 90 days of initial breast conserving surgery, NSW, Australia, 2002-2013
Online Resource 4	Area- and hospital-level variance (σ^2) and the proportional change in variance (%) between baseline and subsequent models, for any reoperation, and separately, for re-excision or mastectomy
Online Resource 5	Adjusted odds ratios for any reoperation versus no reoperation, and separately, for re-excision or mastectomy versus no reoperation within 90 days of initial breast conserving surgery, NSW, Australia 2002-2013
Online Resource 6	Adjusted odds ratios for mastectomy versus re-excision in women undergoing reoperation (n=10,018) within 90 days of initial breast conserving surgery, NSW, Australia 2002-2013

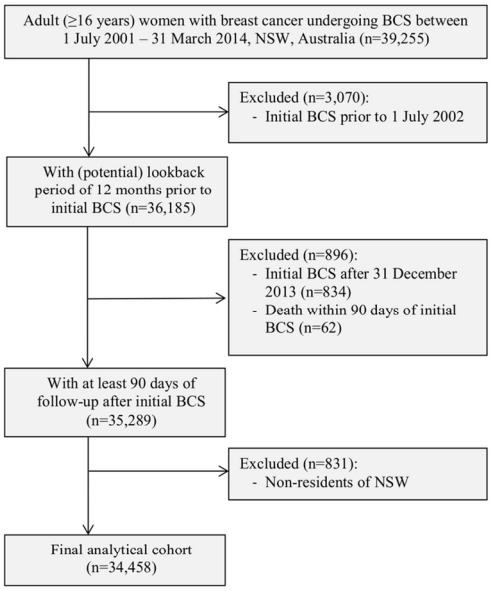

Figure 1

Flow diagram showing study inclusion and exclusion criteria

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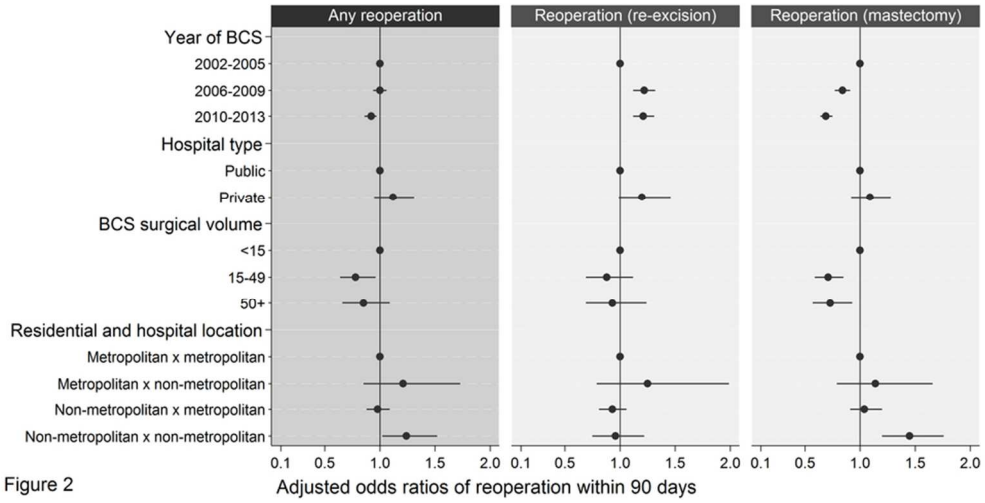

Figure 2

Adjusted odds ratios for any reoperation versus no reoperation, and separately, for re-excision or mastectomy versus no reoperation within 90 days of initial breast conserving surgery, NSW, Australia, 2002-2013. Shows ORs for calendar year and health system-level factors fully adjusted for patient-level and area-level contextual factors based on multilevel, cross-classified binomial (any reoperation) and multinomial (re-excision, mastectomy) logistic regression models.

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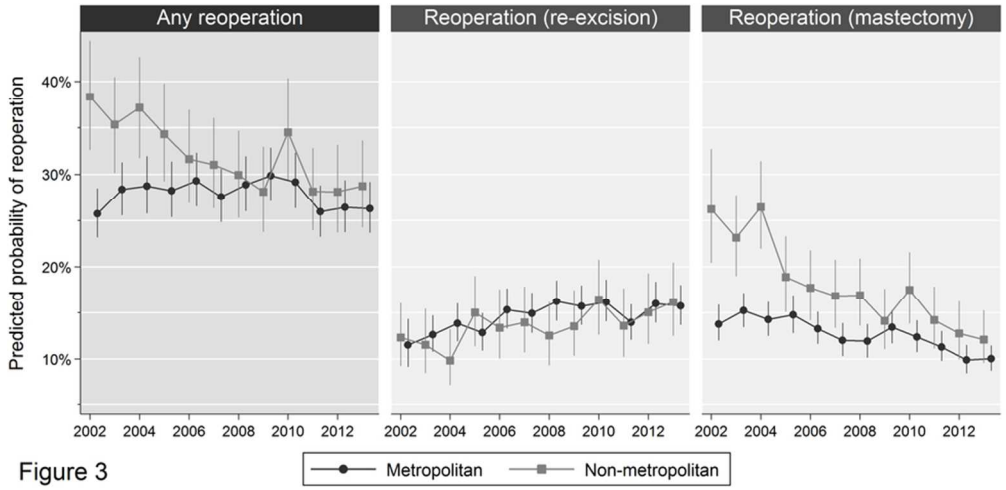

Figure 3

Population-averaged predicted probabilities of any reoperation, and separately, of re-excision or mastectomy, within 90 days of initial breast conserving surgery, by calendar year and location, NSW, Australia, 2002-2013. Predicted probabilities obtained from fully adjusted multilevel, cross-classified binomial (any reoperation) and multinomial (re-excision, mastectomy) logistic regression models containing interaction terms between discrete calendar years geographic location. For illustrative purposes, graph restricted to concordant metropolitan or non-metropolitan residential and hospital location.

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ONLINE RESOURCES

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Online Resource 6	Adjusted odds ratios for mastectomy versus re-excision in women undergoing reoperation (n=10,018) within 90 days of initial breast conserving surgery, NSW, Australia 2002-2013

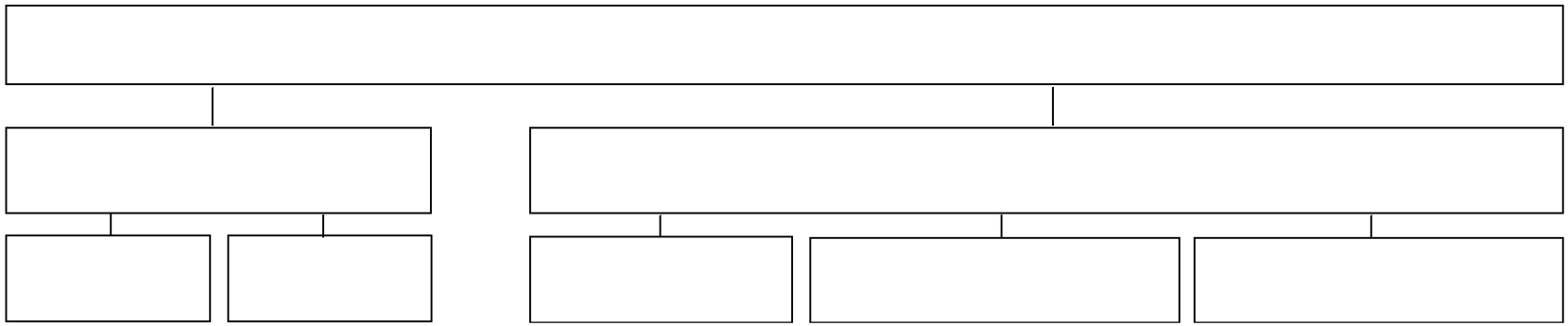
Online Resource 1 Australian Classification of Health Interventions (ACHI) procedure codes

Type of surgery	ACHI Block	ACHI Codes	Description
Breast conserving surgery	1744	30347-00, 31500-00	Excision of lesion of breast
		30342-00	Local excision of lesion of breast
		30346-00	Local excision of lesion of breast with frozen section biopsy
	1745	30342-01	Segmental resection of breast
		30346-01	Segmental resection of breast with frozen section biopsy
	1746	30350-00	Partial mastectomy
		30350-01	Partial mastectomy with frozen section biopsy
Re-excision	1744	30348-00, 31515-00	Re-excision of lesion of breast
Mastectomy	1747	30356-03	Subcutaneous mastectomy with frozen section biopsy, bilateral
		30356-01	Subcutaneous mastectomy with frozen section biopsy, unilateral
		30356-02, 30354-01, 31524-01	Subcutaneous mastectomy, bilateral
		30356-00, 30354-00, 31524-00	Subcutaneous mastectomy, unilateral
	1748	30338-03	Simple mastectomy with frozen section biopsy, bilateral
		30338-01	Simple mastectomy with frozen section biopsy, unilateral
		30338-02, 30351-01, 31518-01	Simple mastectomy, bilateral
		30338-00, 30351-00, 31518-00	Simple mastectomy, unilateral
	1749	30353-03	Extended simple mastectomy with frozen section biopsy, bilateral
		30353-01	Extended simple mastectomy with frozen section biopsy, unilateral
		30353-02	Extended simple mastectomy, bilateral
		30353-00	Extended simple mastectomy, unilateral
	1750	30359-03	Modified radical mastectomy with frozen section biopsy, bilateral
		30359-01	Modified radical mastectomy with frozen section biopsy, unilateral
		30359-02	Modified radical mastectomy, bilateral
		30359-00	Modified radical mastectomy, unilateral
	1751	30359-07	Radical mastectomy with frozen section biopsy, bilateral
		30359-05	Radical mastectomy with frozen section biopsy, unilateral
		30359-06	Radical mastectomy, bilateral
		30359-04	Radical mastectomy, unilateral

Online Resource 2 Distribution of hospitals and patients by hospital type, surgical volume and hospital location

	Distribution of hospitals		Distribution of patients	
	Metropolitan	Non-metropolitan	Metropolitan	Non-metropolitan
Variable	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Hospital type	p=0.003[a]		p<0.001[a]	
Public	35 (42.2)	51 (65.4)	11,402 (42.9)	4,114 (52.1)
Private	48 (57.8)	27 (34.6)	15,157 (57.1)	3,785 (47.9)
BCS surgical volume[b]	p<0.001[a]		p<0.001[a]	
<1	20 (24.1)	33 (42.3)	58 (0.2)	98 (1.2)
1-4	6 (7.2)	15 (19.2)	128 (0.5)	397 (5.0)
5-14	15 (18.1)	12 (15.4)	1,232 (4.6)	1,365 (17.3)
15-49	24 (28.9)	17 (21.8)	6,844 (25.8)	5,380 (68.1)
50-99	10 (12.1)	1 (1.3)	6,782 (25.5)	659 (8.3)
100+	8 (9.6)	0 (0.0)	11,515 (43.4)	0 (0.0)
Total	83 (100.0)	78 (100.0)	26,559 (100.0)	7,899 (100.0)

Abbreviations: BCS, breast conserving surgery.
[a]*p*-values from Pearson's $\chi 2$ test.
[b]Average annual BCS cases per hospital, 2002-2013.



Online Resource 4 **Area- and hospital-level variance (σ^2) and the proportional change in variance (%) between baseline and subsequent models, for any reoperation versus no reoperation, and separately, for re-excision or mastectomy versus no reoperation[a]**

		Any reoperation				Reoperation (re-excision)				Reoperation (mastectomy)			
Model	**Variables**	**σ**	**SE of σ**	**p-value**	**PCV**	**σ**	**SE of σ**	**p-value**	**PCV**	**σ**	**SE of σ**	**p-value**	**PCV**
Random intercept for hospital													
Baseline	Age-group	0.174	0.033	0.000		0.194	0.037	0.000		0.208	0.041	0.000	
Model 2	+ Aboriginal status, country of birth	0.176	0.033	0.000	-1.1	0.195	0.038	0.000	-0.5	0.215	0.044	0.000	-3.4
Model 3	+ tumour type, previous cancer, comorbidities	0.179	0.034	0.000	-2.9	0.197	0.039	0.000	-1.5	0.214	0.043	0.000	-2.9
Model 4	+ calendar year	0.177	0.033	0.000	-1.7	0.204	0.040	0.000	-5.2	0.200	0.040	0.000	3.8
Model 5	+ area-level socioeconomic status	0.178	0.033	0.000	-2.3	0.203	0.039	0.000	-4.6	0.196	0.039	0.000	5.8
Model 6	+ hospital type, BCS surgical volume	0.156	0.031	0.000	10.3	0.201	0.040	0.000	-3.6	0.156	0.033	0.000	25.0
Model 7	+ combined residential and hospital location	0.148	0.030	0.000	14.9	0.201	0.041	0.000	-3.6	0.125	0.028	0.000	39.9
Model 7a	Model 7 + interaction calendar year, location [b]	0.143	0.029	0.000	17.8	0.196	0.042	0.000	-1.0	0.122	0.028	0.000	41.3
Model 7b	Model 7 + interaction calendar year, surgical volume [b]	0.144	0.028	0.000	17.2	0.197	0.041	0.000	-1.5	0.124	0.029	0.000	40.4
Random intercept for SLA													
Baseline	Age-group	0.002	0.002	0.179		0.010	0.004	0.008		0.007	0.003	0.017	
Model 2	+ Aboriginal status, country of birth	0.002	0.001	0.115	0.0	0.010	0.004	0.007	0.0	0.007	0.003	0.014	0.0
Model 3	+ tumour type, previous cancer, comorbidities	0.002	0.001	0.222	0.0	0.010	0.003	0.005	0.0	0.008	0.003	0.011	-14.3
Model 4	+ calendar year	0.002	0.002	0.210	0.0	0.010	0.004	0.007	0.0	0.007	0.003	0.010	0.00
Model 5	+ area-level socioeconomic status	0.002	0.002	0.198	0.0	0.010	0.004	0.013	0.0	0.007	0.003	0.012	0.00
Model 6	+ hospital type, BCS surgical volume	0.003	0.002	0.160	-50.0	0.009	0.004	0.017	10.0	0.004	0.002	0.035	42.9
Model 7	+ combined residential and hospital location	0.003	0.002	0.148	-50.0	0.009	0.004	0.011	10.0	0.002	0.002	0.191	71.4
Model 7a	Model 7 + interaction calendar year, location [b]	0.002	0.002	0.214	0.0	0.009	0.004	0.012	10.0	0.001	0.001	0.199	85.7
Model 7b	Model 7 + interaction calendar year, surgical volume [b]	0.002	0.002	0.156	0.0	0.010	0.004	0.021	0.0	0.001	0.001	0.115	85.7

Abbreviations: SE, standard error; PCV, proportional change in variance; SLA, statistical local area; BCS, breast conserving surgery.

[a] Multilevel, cross-classified binomial (any reoperation) and multinomial (re-excision, mastectomy) logistic regression models.

[b] Calendar year modelled as a continuous variable in interaction model.

Online Resource 5 **Adjusted odds ratios for any reoperation versus no reoperation, and separately, for re-excision or mastectomy versus no reoperation within 90 days of initial breast conserving surgery, NSW, Australia 2002-2013[a]**

	Any reoperation	Reoperation (re-excision)	Reoperation (mastectomy)
Characteristic	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Age (years)			
<35	1.22 (1.02-1.47)	0.91 (0.71-1.17)	1.60 (1.28-2.01)
35-49	1.41 (1.33-1.49)	1.24 (1.15-1.34)	1.61 (1.48-1.74)
50-64	1.00	1.00	1.00
65-79	0.89 (0.83-0.94)	0.82 (0.76-0.89)	0.96 (0.89-1.04)
80+	0.51 (0.45-0.58)	0.37 (0.30-0.44)	0.69 (0.59-0.80)
Aboriginal status			
Non-Aboriginal	1.00	1.00	1.00
Aboriginal	1.13 (0.88-1.47)	0.87 (0.60-1.25)	1.40 (1.03-1.89)
Country of birth			
Australia/New Zealand	1.00	1.00	1.00
Europe	1.02 (0.95-1.09)	0.99 (0.90-1.09)	1.04 (0.94-1.14)
East Asia	1.22 (1.10-1.35)	1.15 (1.02-1.31)	1.29 (1.13-1.47)
Other	1.01 (0.92-1.10)	1.02 (0.91-1.14)	0.99 (0.88-1.13)
Unknown	0.94 (0.80-1.11)	0.94 (0.76-1.16)	0.95 (0.76-1.18)
Tumour type			
Invasive	1.00	1.00	1.00
Insitu/mixed	1.81 (1.72-1.91)	1.76 (1.64-1.89)	1.86 (1.74-1.99)
Previous breast cancer[b]			
No	1.00	1.00	1.00
Yes	0.55 (0.40-0.78)	0.52 (0.33-0.83)	0.58 (0.38-0.90)
Other previous cancer[b]			
No	1.00	1.00	1.00
Yes	0.85 (0.64-1.13)	0.74 (0.50-1.10)	0.95 (0.67-1.35)
Number of comorbidities[b]			
No comorbidities	1.00	1.00	1.00

Characteristic	Any reoperation OR (95% CI)	Reoperation (re-excision) OR (95% CI)	Reoperation (mastectomy) OR (95% CI)
1 comorbidity	0.91 (0.82-1.01)	0.89 (0.77-1.02)	0.93 (0.82-1.07)
2 comorbidities	1.01 (0.78-1.31)	0.82 (0.57-1.18)	1.17 (0.86-1.60)
3+ comorbidities	0.68 (0.42-1.12)	0.64 (0.31-1.31)	0.69 (0.36-1.33)
Year of BCS			
2002-2005	1.00	1.00	1.00
2006-2009	1.00 (0.94-1.06)	1.22 (1.12-1.32)	0.84 (0.77-0.91)
2010-2013	0.92 (0.86-0.97)	1.21 (1.12-1.31)	0.69 (0.64-0.75)
Index of relative socioeconomic disadvantage[c]			
Quintile 5 (Least disadvantaged)	1.00	1.00	1.00
Quintile 4	1.03 (0.94-1.11)	1.03 (0.92-1.15)	1.01 (0.91-1.12)
Quintile 3	0.97 (0.89-1.07)	0.94 (0.83-1.07)	0.99 (0.89-1.11)
Quintile 2	1.02 (0.91-1.14)	1.02 (0.87-1.19)	1.02 (0.89-1.16)
Quintile 1 (Most disadvantaged)	1.03 (0.93-1.15)	1.07 (0.93-1.23)	0.99 (0.87-1.12)
Hospital type			
Public	1.00	1.00	1.00
Private	1.12 (0.95-1.31)	1.20 (0.99-1.46)	1.09 (0.92-1.28)
BCS surgical volume[d]			
<15	1.00	1.00	1.00
15-49	0.78 (0.64-0.96)	0.88 (0.69-1.12)	0.71 (0.59-0.85)
50+	0.85 (0.66-1.09)	0.93 (0.69-1.24)	0.73 (0.57-0.93)
Residential and hospital location			
Metropolitan x metropolitan	1.00	1.00	1.00
Metropolitan x non-metropolitan	1.21 (0.85-1.73)	1.25 (0.79-1.99)	1.14 (0.79-1.66)
Non-metropolitan x metropolitan	0.98 (0.88-1.09)	0.93 (0.81-1.06)	1.04 (0.91-1.20)
Non-metropolitan x non-metropolitan	1.24 (1.02-1.52)	0.96 (0.75-1.22)	1.45 (1.20-1.76)

Abbreviations: OR, odds ratio; CI, confidence interval; BCS, breast conserving surgery.

[a] ORs obtained from multilevel, cross-classified binomial (any reoperation) and multinomial (re-excision, mastectomy) logistic regression models, adjusted for patient-level factors, calendar year, area-level contextual factors, and health system-level factors.

[b] Recorded on or within 12 months prior to initial BCS.

[c] Index of relative socioeconomic disadvantage for statistical local area of residence.

[d] Average annual number of BCS cases per hospital, 2002-2013.

Online Resource 6 **Adjusted odds ratios for mastectomy versus re-excision in women undergoing re-operation within 90 days of initial breast conserving surgery, NSW, Australia 2002-2013[a]**

Characteristic	Mastectomy (versus re-excision) OR (95% CI)
Age (years)	
<35	1.78 (1.31-2.42)
35-49	1.29 (1.17-1.43)
50-64	1.00
65-79	1.17 (1.05-1.29)
80+	1.87 (1.47-2.37)
Aboriginal status	
Non-Aboriginal	1.00
Aboriginal	1.60 (1.03-2.49)
Country of birth	
Australia/New Zealand	1.00
Europe	1.03 (0.91-1.17)
East Asia	1.10 (0.94-1.28)
Other	0.99 (0.84-1.16)
Unknown	1.02 (0.77-1.33)
Tumour type	
Invasive	1.00
Insitu/mixed	1.06 (0.98-1.16)
Previous breast cancer[b]	
No	1.00
Yes	1.12 (0.61-2.08)
Other previous cancer[b]	
No	1.00
Yes	1.38 (0.84-2.26)
Number of comorbidities[b]	
No comorbidities	1.00

Characteristic	Mastectomy (versus re-excision) OR (95% CI)
1 comorbidity	1.06 (0.88-1.27)
2 comorbidities	1.52 (0.96-2.40)
3+ comorbidities	1.19 (0.47-3.02)
Year of BCS	
2002-2005	1.00
2006-2009	0.69 (0.63-0.77)
2010-2013	0.57 (0.51-0.63)
Index of relative socioeconomic disadvantage[c]	
Quintile 5 (Least disadvantaged)	1.00
Quintile 4	1.00 (0.88-1.14)
Quintile 3	1.06 (0.92-1.23)
Quintile 2	1.01 (0.85-1.20)
Quintile 1 (Most disadvantaged)	0.94 (0.80-1.10)
Hospital type	
Public	1.00
Private	0.90 (0.77-1.07)
BCS surgical volume[d]	
<15	1.00
15-49	0.81 (0.67-0.98)
50+	0.79 (0.63-0.99)
Residential and hospital location	
Metropolitan x metropolitan	1.00
Metropolitan x non-metropolitan	0.88 (0.60-1.29)
Non-metropolitan x metropolitan	1.15 (0.97-1.36)
Non-metropolitan x non-metropolitan	1.49 (1.23-1.80)

Abbreviations: OR, odds ratio; CI, confidence interval; BCS, breast conserving surgery.
[a] ORs obtained from multilevel, cross-classified binomial (mastectomy versus re-excision) logistic regression models in women undergoing reoperation (n=10,018), adjusted for patient-level factors, calendar year, area-level contextual factors, and health system-level factors.
[b] Recorded on or within 12 months prior to initial BCS.
[c] Index of relative socioeconomic disadvantage for statistical local area of residence.
[d] Average annual number of BCS cases per hospital, 2002-2013.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	1, 3
Objectives	3	State specific objectives, including any prespecified hypotheses	1, 3
Methods			
Study design	4	Present key elements of study design early in the paper	1, 3, 4-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-7
Bias	9	Describe any efforts to address potential sources of bias	6-7, 11-12
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6-7
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4
		(b) Give reasons for non-participation at each stage	4
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	8, Table 1
		(c) Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	Report numbers of outcome events or summary measures over time	8, Table 2, Online Resource 3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2
		(*b*) Report category boundaries when continuous variables were categorized	5-6, all tables and figures
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	6, Table 2
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Fig 2-3, Online Resources
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.