BMJ Open

# Monitoring TNM stage of female breast cancer and survival across the South Australian population, with national and international TNM benchmarking

| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2020-037069 |
| Article Type: | Original research |
| Date Submitted by the Author: | 17-Jan-2020 |
| Complete List of Authors: | Li, Ming; University of South Australia, Cancer Research Institute<br>Roder, David; University of South Australia, Cancer Research Institute; Cancer Institute NSW<br>D'Onise, Katina; SA Health Department for Health and Wellbeing, Prevention and Population Health<br>Walters, David; The Queen Elizabeth Hospital, Department of Surgery; The University of Adelaide, Faculty of Health and Medical Sciences<br>Farshid, Gelareh; SA Pathology; The University of Adelaide, Faculty of Health and Medical Sciences<br>Buckley, Elizabeth; University of South Australia, Cancer Research Institute<br>Karapetis, Chris; Flinders University, Medical Oncology<br>Joshi, Rohit; The University of Adelaide, Faculty of Health and Medical Sciences; Adelaide Oncology and Haematology, Cancer Research and Clinical Trials<br>Price, Timothy ; The University of Adelaide, Faculty of Health and Medical Sciences; The Queen Elizabeth Hospital, Clinical Cancer Research<br>Townsend, Amanda; The Queen Elizabeth Hospital, Clinical Cancer Research; Basil Hetzel Institute for Translational Health Research<br>Miller, Caroline; South Australian Health and Medical Research Institute, Health Policy Centre; The University of Adelaide, Faculty of Health and Medical Sciences<br>Currow, David; Cancer Institute NSW<br>Powell, Kate; South Australian Health and Medical Research Institute, Health Policy Centre; SA Health Department for Health and Wellbeing, SA Clinical Cancer Registry<br>Buranyi-Trevarton, Dianne; SA Health Department for Health and Wellbeing, SA Clinical Cancer Registry<br>Olver, Ian; The University of Adelaide, Faculty of Health and Medical Sciences |
| Keywords: | Breast tumours < ONCOLOGY, Epidemiology < ONCOLOGY, PUBLIC HEALTH |
| | |

*I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.*

*The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.*

*Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.*

# Monitoring TNM stage of female breast cancer and survival across the South Australian population, with national and international TNM benchmarking

Ming Li[1], David Roder[1, 11]*, Katina D'Onise[2], David Walters[3, 7], Gelareh Farshid[4, 7], Elizabeth Buckley[1], Chris Karapetis[5], Rohit Joshi[6, 7], Tim Price[7, 8], Amanda Townsend[8, 9], Caroline Miller[7, 10], David Currow[11], Kate Powell[10, 12], Dianne Buranyi-Trevarton[12], Ian Olver[7]

[1] Cancer Research Institute, University of South Australia, Adelaide, South Australia, Australia

[2] Prevention and Population Health, SA Health Department for Health and Wellbeing, Adelaide, South Australia, Australia

3 Department of Surgery, Queen Elizabeth Hospital, Woodville South, South Australia, Australia

4 SA Pathology, Adelaide, South Australia, Australia

5 Medical Oncology, Flinders University, Bedford Park, South Australia, Australia

6 Cancer Research and Clinical Trials, Adelaide Oncology and Haematology, North Adelaide, South Australia, Australia

7 Faculty of Health and Medical Sciences, University of Adelaide, Adelaide, South Australia, Australia

8 Clinical Cancer Research, Queen Elizabeth Hospital, Woodville South, South Australia, Australia

9 Basil Hetzel Institute for Translational Health Research, Woodville South, South Australia, Australia

10 Health Policy Centre, South Australian Health & Medical Research Institute (SAHMRI), Adelaide, South Australia, Australia

11 Cancer Institute NSW, Eveleigh, New South Wales, Australia

12 SA Clinical Cancer Registry, South Australian Department for Health and Wellbeing, Adelaide, South Australia, Australia

*** Corresponding author:** David Roder

Mobile: 0478 408 386

Office: 08 8302 2640

Email: David.roder@unisa.edu.au

Postal address:

University of South Australia

Cancer Research Institute (CWE-48)

GPO Box 2471

Adelaide SA 5001

**Abstract:**

**Objective:** Using linked cancer registry and administrative data to monitor Tumour, Node and Metastases (TNM) stage and survival from female breast cancer in Australia.

**Method:** Analysis of 2000-2014 diagnoses with linked population-based data to investigate: (1) sociodemographic predictors of advanced stage (stages III & IV), using unadjusted and adjusted logistic regression; and (2) sociodemographic factors and stage as predictors of breast-cancer survival using competing risk regression.

**Design:** Population-based registry cohort

**Setting and participants:** 14759 South Australian women diagnosed in 2000-2014

**Primary and secondary outcome measures:** Stage and survival

**Results:** At diagnosis, 46% of women were classified as stage I, 39% as stage II, 12% as stage III, and 4% as stage IV. After adjusting for sociodemographic factors, advanced stage was more common: (a) for ages <50 years; and although not statistically significant, for ages 80+ years; and (b) in women from socioeconomically disadvantaged areas. Compared with 2000-2004 diagnoses, stage and sociodemographic adjusted risks (sub-hazard ratios - SHR) of breast cancer death were lower in 2005-2009 (SHR: 0.75, 95% CI: 0.67-0.83) and 2010-2015 (SHR: 0.57, 95% CI: 0.48-0.67). Compared with stage I, the SHR was 3.87 (95% CI: 3.32-4.53) for stage II, 10.87 (95% CI: 9.22-12.81) for stage III, and 41.97 (95% CI: 34.78-50.65) for stage IV. Women aged 70+ years at diagnosis and those living in the most socioeconomically disadvantaged areas were at elevated risk of breast cancer death, independent of stage and sociodemographic factors.

**Conclusions:** Stage varied by age, diagnostic period, and socioeconomic status, and was a stronger predictor of survival than other statistically significant predictors (i.e., age, diagnostic period and socioeconomic status). Achieving earlier diagnosis outside the original BreastScreen target of 50-69 years (as applying <2014) and in residents of socioeconomically disadvantaged areas likely would increase cancer survival at a population level.

**Key words:** breast cancer; cancer stage; cancer survival; South Australia

**Word Count:** 3037 words

**Article Summary:**

**Strengths and Limitations**

Strengths:

- Shows the utility of readily available registry and administrative data for population-based monitoring of TNM stage

- Shows the face validity of these TNM stage distributions through comparisons with data from special studies and international benchmarks
- Shows plausible predictive effects of stage on survival

Limitations:

- Study limited to broad TNM categories due to limited detail available
- Use of AJCC 7th Revision with further adaptation required for the 8th Revision

**Introduction:**

Breast cancer is the most common cancer recorded in Australian women by population registries (1). The 5-year relative survival from female breast cancer increased markedly from 72% in 1984-1988 to 91% in 2011-2015 (1). This increase was attributed mostly to treatment advances and earlier cancer detection largely effected by the national population screening program established in 1991 following several pilot projects (1, 2). The screening program offered 2-yearly screening mammograms to women in the target age range of 50-69 years, with an extension to 74 years from 2014 (1, 2). Women aged 40-49 years, in particular women with a strong family history and those older than the screening target, were eligible for screening but not actively invited (1, 2).

Anatomic stage of cancer at diagnosis is a key predictor of cancer survival (3, 4). The Tumour, Node and Metastases (TNM) staging system is a gold standard for staging most solid cancers in clinical practice and can be used, with minor modification, to monitor stage at a population level using data available to cancer registries (5). TNM stage was determined at a population level by population registries for 95% of female breast cancers diagnosed in Australia in a one-off study in 2011 funded through Cancer Australia (5). This followed an earlier Victorian pathfinder study for methodological development (6). Staging data are useful to service planners as indicators of need, to assess alignment of patterns of care with recommended care, to evaluate survival outcomes, to design interventions to address disparities, and to evaluate the population impact of new adjuvant and other therapies by stage.

Stage was derived in the present study for 14759 women with invasive breast cancer (96% of diagnoses), primarily using pathology and hospital reporting, and checked with aggregated statistical profiles from the Breast Quality Audit (BQA) of Breast Surgeons of Australia and New Zealand (BSURGANZ) (7). For consistency, the staging process followed national guidelines developed in Victoria for population-based registries and used previously in a 2011 national study (5, 6). Stage was broadly classified as stage I, II, III or IV, according to criteria of the American Joint Committee on Cancer (AJCC, 7th Revision), to reduce inconsistencies in time series from changes in detail from AJCC revisions (8).

We use linked registry and administrative data to investigate sociodemographic predictors of advanced breast cancer stage, and together with stage, the sociodemographic predictors of invasive breast cancer survival in the South Australian female population.

**Methods:**

*Study design and data linkage*

Population-based invasive breast cancer data (ICD-O-3 C50) obtained from the South Australian Cancer Registry (SACR) for 2000-2014 diagnoses comprised the main linkage spine. Operations of

the SACR have been described previously (9). All invasive cancers diagnosed in South Australia are recorded, except non-melanoma cancers of the skin, using international registry standards (9, 10). Reporting by pathology laboratories and hospitals is a legal requirement (9).

For each cancer, the SACR records the primary site, morphology, diagnosis date, and the woman's country of birth, death date and cause, and postcode-derived relative socioeconomic disadvantage and geographic remoteness (9). The Registry of Births, Deaths and Marriages, the Australian Bureau of Statistics (ABS) and National Death Index (NDI) are used as sources of death data, including cause of death expressed by cancer type or as non-cancer (9).

For consistency, staging followed as closely as possible the process used in the earlier pilot and national study (5, 6). Stage was derived from pathology and hospital reporting and stage distributions checked with statistical profiles from the Breast Quality Audit (BQA) of Breast Surgeons of Australia and New Zealand (BSURGANZ) (7). Data on breast tumour diameter and nodal status were available through the SA Cancer Registry and distant metastases were indicated by inpatient diagnosis codes. SA Clinical Cancer Registry data for major public hospitals were used for validity checking and to fill gaps. Receptor status and other biomarkers were not addressed as these characteristics were not routinely recorded by Australian population-based registries for the study period and were not included in the national TNM staging protocol developed for population-wide monitoring purposes (5).

Linkage of SACR and hospital inpatient data was predominantly through South Australia Northern Territory DataLink using probabilistic matching of identifiers (name, sex, date of birth and address) (11, 12). This process followed the principle of separating patient identifiers from clinical content data to protect privacy (12). Ethics approval for the study was obtained from research ethics committees of the South Australian Health Department (SA Health: HREC/17/SAH/38); University of South Australia (UNISA; 200021), and Australian Institute of Health and Welfare (AIHW: EO2017/3/361).

*Other study variables*

Age at diagnosis was classified as: <50, 50-59, 60-69, 70-79 or 80+ years; and country of birth as Australia, other predominantly English-speaking country or predominantly non-English speaking country, as described previously (13, 14). Socio-economic status was derived from residential postcode at diagnosis using the Socioeconomic Index for Areas (SEIFA) Index of Relative Socio-economic Disadvantage (IRSD) expressed in quintiles (15). Residential area was classified as a major city, inner regional, outer regional, remote or very remote area, using the Australian Standard Geographical Classification (ASGC) Remoteness index (16). Diagnostic period was categorized as 2000–2004, 2005–2009, and 2010–2014.

*Statistical analysis*

Breast cancer stage was analysed by population characteristic using analysis of variance (ANOVA) for age and conventional chi-square or corresponding ranked tests depending on variable distributions (17, 18). Advanced cancer stage (stage III or IV) as opposed to early stage (stage I or II) was analysed by sociodemographic descriptors using unadjusted and socio-demographically adjusted logistic regression (17, 18).

Deaths were classified as attributed to breast cancer, as compared with another cancer or other causes, and predictors of survival outcomes from breast cancer were analysed for a follow-up period to death on December 31st, 2014, whichever came first. The predictors of breast cancer death were investigated using competing risk regression models (Stata module "stcrreg") (18, 19). Deaths from causes other than breast cancer were regarded as the competing risk. Unadjusted predictors were explored, plus predictors adjusted for stage and sociodemographic characteristics. Reference categories for dummy variables were the first categories listed for the respective characteristics in Tables 1.

Analyses were conducted using Stata 14 (StataCorp, College Station, Texas, USA), with statistical significance set at $p<0.05$. All survival analyses used complete case data.

**Results:**

*Population description:*

The mean age of the 14759 staged cases was 61 years; 53% were aged 50-69 years (Table 1). For women of known country of birth, 70% were born in Australia, a further 17% were born in other predominantly English-speaking countries, and the other 13% were born in predominantly non-English-speaking countries. Almost three quarters (74%) resided in a major city area, 11% in inner regional locations, and 14% in outer regional or remote/very remote areas. The percentage of women by residential socioeconomic disadvantage status ranged from 17% for the most disadvantaged to 22% for the least disadvantaged quintile. The percentage by diagnostic period increased from 31% for 2000-2004 to 35% both for 2005-2009 and 2010-2014.

*Cancer stage:*

The percentage distribution by TNM stage was: stage I, 46%; stage II, 39%; stage III, 12%; and stage IV, 4%. Differences in stage were found in unadjusted analysis by age ($p<0.001$), country of birth ($p=0.002$), and SEIFA disadvantage ($p<0.001$), but not by residential remoteness ($p=0.310$) or diagnostic period ($p=0.346$) (Table 1).

In adjusted analyses, and when compared with women aged <50 years at diagnosis, the adjusted odds ratio (OR) for advanced stage was: 0.70 (95% CI 0.62-0.80) for ages 50-59 years, 0.60 (95% CI 0.53-0.69) for ages 60-69 years, and 0.85 (95% CI 0.74-0.98) for ages 70-79 years. Higher adjusted risk of

advanced stage tended occur in ages <50 years and 80+ years, although the difference for women age 80+ years compared with <50 years did not achieve statistical significance (OR: 1.11 95% CI: 0.95-1.31).

The adjusted odds ratio for advanced cancer were lower among women of least residential socioeconomic disadvantage (Q4/Q5) than most disadvantage (Q1) (OR 0.79 95% CI 0.68-0.92) for Q4 and OR 0.75 (95% CI: 0.65-0.87) for Q5 (least disadvantage). The risk of having advanced stage did not differ in adjusted analyses by country of birth or residential remoteness (Table 2).

While the adjusted odds ratio for advanced cancer was higher in 2005-2009 than the 2000-04 baseline (OR 1.20 95% CI: 1.07-1.34), the difference between 2010-14 and 2000-04 was not significant (OR 1.05 95%CI: 0.95-1.19).

Analyses across age categories showed heterogeneity of odds ratios for advanced stage by diagnostic period. The odds ratio for advanced cancer stage among women aged 80+ years varied significantly by period. During 2000-2004, women aged 80+ years were significantly more likely to have advanced stage than those in the reference age (<50 years) (OR 1.50 95% CI: 1.12-2.01) but significant corresponding associations were not observed in 2005-2009 (OR 1.16 95% CI: 0.90-1.50) or 2010-2014 (OR 0.82 95% CI: 0.62-1.10).

*Breast cancer mortality:*

Of the cohort of 14759 women, 2924 (19.8%) had died from any cause and 1740 (11.8%) from breast cancer by the end of the study period (Table 1). Adjusted sub-hazard ratios (Table 3) varied by: (1) stage – increasing with more advanced stage to 41.97 (95% CI 34.78-50.65) for stage IV compared with stage 1; (2) age at diagnosis – increasing with age to 2.24 (95% CI 1.88-2.66) for age 80+ compared with <50 years; and (3) residential socioeconomic disadvantage – reducing to 0.73 (95% CI 0.62-0.87) for the least disadvantaged compared with most disadvantaged quintile. The adjusted risk of breast cancer death also reduced, independent of stage and sociodemographic factors, in the later diagnostic periods compared with the 2000-2004 reference (SHR 0.75 95% CI: 0.67-0.83) for 2005-2009 and 0.57 (95% CI 0.48-0.67) for 2010-2014. Significant differences were not found in unadjusted or adjusted analyses by country of birth or residential remoteness.

**Discussion:**

Results show a very similar stage distribution for staged invasive female breast cancers in South Australia in 2000-2014 to that found nationally in the Australian national study for 2011 diagnoses (5). This may reflect the common guidelines and standards for screening and treatment programs occurring across Australia, common accreditation processes, and similar although not identical program participation (20-22) (e.g., 2014-2015 data indicate that approximately 58% of women aged

50-74 years participated in the screening program in South Australia compared with a slightly lower 54% for Australia overall (20)).

Stage distributions were also similar in the present South Australian study to distributions of staged breast cancers in Canada and England (5). The stage distribution in South Australia in 2000-2014 compared with those seen for staged cases in Australia in 2011, Canada in 2013 and England in 2012 were: (1) for stage I - 46% compared with 46%, 47% and 44% respectively; (2) for stage II - 39% compared with 37%, 35% and 39% respectively; (3) for stage III - 12% compared with 13%, 12% and 10% respectively; and (4) for stage IV - 4% compared with 5%, 6% and 7% respectively (5).

We consider these differences to be minor and smaller than anticipated, given potential effects of methodological and geographic differences (5). These factors and differences in diagnostic years may have contributed to the marginally higher proportion of early stage I and II of 85% for South Australia compared with 82% for Australia, although the marginally higher screening participation rates in South Australia may also have contributed (20, 21).

The proportion with advanced cancers (stage III or IV) was lower in the age range of 50-79 years than for younger or older women. A similar pattern was seen for staged cancers in Australia in 2011 where the age-standardized percentage with stage III or IV was 16% compared with 21% for younger and 25% for older women (5). This pattern likely reflects the targeting of women aged 50-69 years for screening nationally during 2000-2013 and the availability of ongoing screening on demand from 70 years of age during the study period (1, 2). In addition, older women aged 80+ years, through a higher prevalence of frailty and comorbidity than for younger women, may have been slower to access clinical services (5). Notably a higher odds ratio for advanced cancers presented in the 80+ year age range than in younger women in 2000-2014, although this was less obvious for the later diagnostic periods and especially for 2010-2014, potentially reflecting a growing emphasis on earlier diagnoses in older women than previously (22).

The proportion of women with breast cancer in the present study ranged from 17% for the most disadvantaged quintile to 22% for the least disadvantaged, which is consistent with the Australia-wide gradient in breast cancer risk by quintile in 2010-2014 (5). Residents of the most disadvantaged quintile were at higher risk of advanced cancers than those from the least disadvantaged quintile in this study, which is confirmatory of the difference found nationally in 2011 (21% vs 16%) (5). Screening participation could have contributed, in that it was reported to be lower for residents of disadvantaged compared with advantaged areas (5). Although screening services have introduced initiatives to address the needs of women from disadvantaged areas, more research into barriers and opportunities would be desirable. Similar sociodemographic disadvantage is evident from national surveys of health behaviour, as relating for example to prevalence of tobacco smoking, overweight and obesity, which likely would compound broader disadvantages experienced by these groups (5).

The absence of differences in risk of advanced stages in our study by residential remoteness may reflect at least in part the use of mobile clinics to take screening services to rural areas. Notably, differences also appeared to be small in the national survey of 2011, with 18% of staged cases having advanced cancers among major city residents compared with 17% among residents of regional areas and 20% for those in remote and very remote areas (5). The absence of a difference in risk by country of birth in the present study is reassuring from an equity perspective.

Approximately 20% of the study cohort died from all causes combined during the study period and 12% died of breast cancer. Predictably the proportion dying from breast cancer increased with TNM stage (from 3% for stage I to 70% for stage IV). Adjusted analyses confirmed stage to be the strongest predictor of survival. The National BreastScreen Evaluation Report of 2009, using data sourced from the Victorian Cancer Registry, indicated that the percentage of breast cancers with diameters ≤15mm was higher at 64% in women notified through BreastScreen than the corresponding 39% for other women in the 50-69-year age range, which likely contributed to the BreastScreen-related survival advantage (23). An Expert Panel assembled from 16 countries by the International Agency for Research on Cancer (IARC) reported in 2015 that participation of women aged 50-69 years in mammography screening can reduce the risk of breast cancer death by approximately 40% (24). In addition, the 2011 national study also showed a 5-year relative survival of 91% for 2011-2015 for all stages combined, but with a very strong association with stage and relative survival (note: more than 95% of women with early stages (TNM I and II) survived five years compared with 81% for stage III and 32% for stage IV) (5).

Older age at diagnosis was predictive of lower survival in the present study, both with and without adjustment for stage and other co-variables, with the lowest survival applying to the 80+ year age range. The national study of 2011 diagnoses provided consistent findings with the lowest 5-year relative survival of 81% applying to women aged 75+ years (5).

Socioeconomic status was also predictive in our study with residents of the least disadvantaged areas having the highest survival. This is consistent with national data for 2006-2010 (5). The factors potentially responsible for this difference warrant further study and could include artificial effects of lead time, overdiagnosis and related factors, and also real effects related to differences in health literacy, lower engagement with health protection, and competing pressures on time and resources by level of disadvantage. Also, a tendency for lower screening participation in these areas may have contributed (5).

A major increase in survival outcomes was evident in the more recent diagnostic periods in the present study, which is also seen in the national data where 5-year relative survival increased from 72% in 1984-1988 to 91% in 2010-2014 (5). This may reflect a combination effect of artificial influences from differences in lead time, over diagnosis and related factors, and real benefits from

screening and treatment advances, among them an increased use of specialized breast cancer centres and advances in adjuvant therapies including radiotherapy, chemotherapy, hormone therapy and systemic therapy directed at the human epidermal growth factor receptor 2 (HER2) (24). The more advanced breast-cancer stage distribution for South Australia in 2005-2009 was unexpected and warrants further investigation. These years represented the end of the film-reading era prior to transfer to digital technology. Despite this peak in advanced cases, it is reassuring to see a steady secular increase in survival.

The present study follows the national study of stage in 2011, which included a South Australian component (5). Stage was derived from pathology reporting and hospital reporting and stage distributions were checked with statistical profiles from the Quality Audit of Breast Surgeons of Australia and New Zealand (7). Limitations included restricting stage to four major categories to avoid inconsistencies due to changes at a more detailed level across versions of AJCC TNM coding (22). Further efforts are needed to improve accuracy of staging, although the 96% coverage of invasive cancers achieved with this staging methodology was high and the results were similar to those observed in other studies in Australia, Canada and England (5).

**Conclusions:** Breast cancer stage varies by age, diagnostic period and socioeconomic status. Stage was a stronger predictor of survival outcome than other significant predictors (i.e.: age at diagnosis, diagnostic period, and socioeconomic status). Achieving earlier diagnosis in women outside the original screening target of 50-69 years and in residents of socioeconomically disadvantaged areas likely would further increase cancer survival at a population level. The present data show plausible stage distributions and effects on survival, using readily available data for staging. The uptake of voluntary screening from age of 40 years may improve outcome for patients under 50 years as more targeted screening for patients with genetic risk and breast density may also have positive impacts.

**Declarations:**

**Ethics approval and consent to participate:** Ethics approval for the study was obtained from research ethics committees of the South Australian Health Department (SA Health: HREC/17/SAH/38), University of South Australia (UNISA: 200021), and Australian Institute of Health and Welfare (AIHW: EO2017/3/361).

**Patient consent:** A Waiver of Consent was granted by the research ethics committee and Legal Authorization for data collection without consent was provided under the South Australian Health Care Act. Individual consent to participate was waived due to the absence of identifiers and contact details on the linked data, the size of the study, the need for close to complete participation to avoid statistical bias, and adherence to the separation of clinical data from identifiers to protect privacy. Only aggregated data are presented.

**Patient and Public Involvement:** We did not directly include PPI in this study, but the database used in the study was developed with PPI and is updated by a committee that includes patient representatives.

**Competing Interests:** The authors declare that they have no competing interests.

**Availability of data and materials:** The data used in this study are available from the South Australian Department for Health and Wellbeing (South Australian Cancer Registry & Integrated South Australian Activity Collection). Source data only would be publicly available with the approval of these source data custodians.

**Funding:** This project is supported by a grant from the National Breast Cancer Foundation (CRP-17-001) and Cancer Council's Beat Cancer Project on behalf of its donors and the State Government through the Department of Health.

**Author contributions:** Study concept: DR, ML; Study Design: DR, ML; Data acquisition: DR, DBT, KP; KDO; Data Analysis: ML, DR; Data interpretation: ML, DR, DBT, KP, IO, GF; Manuscript writing: ML, DR; Review of manuscript: ML, DR, KDO, DW, GF, EB, CK, RJ, NS, TP, AT, CM, DC, KP, DBT, IO; All authors read and approved the final version.

**Acknowledgements:** We are grateful to the National Breast Cancer Foundation, the SA Government, Cancer Council South Australia, the Breast Surgeons of Australia and New Zealand and SANT DataLink.

**References:**

1. Australian Institute of Health and Welfare. Cancer in Australia 2019. Cancer series no.119. Cat. no. CAN 123. Canberra: AIHW, 2019.
2. Australian Government, Department of Health. Expansion of BreastScreen Australia. Canberra: Commonwealth of Australia, 2019.
3. McPhail S, Johnson S, Greenberg D, et al. Stage at diagnosis and early mortality from cancer in England. British Journal of Cancer. 2015;112 Suppl 1:S108-15.
4. de Mello Ramirez Medina J, de Araujo Trugilho I, Mendes GNB, et al. Advanced clinical stage at diagnosis of breast cancer is associated with poorer health-related quality of life: a cross-sectional study. European Journal of Breast Health 2019;15(1): 26-31.
5. Cancer Australia. National Cancer Control Indicators. Sydney: Cancer Australia, 2019. Available: https://ncci.canceraustralia.gov.au/ [Accessed 1 October 2019].
6. National Breast and Ovarian Cancer Centre. Breast cancer staging and treatment: Data linkage report. National Breast and Ovarian Cancer Centre, Surry Hills, NSW, 2010.

7. Royal Australasian College of Surgeons (RACS). BreastSurgANZ quality audit. Adelaide: RACS, 2019. Available: https://www.surgeons.org/research-audit/morbidity-audits/morbidity-audits-managed-by-racs/breastsurganz-quality-audit [Accessed 10 October 2019].
8. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and future TNM. Annals of Surgical Oncology 2010; 17(6): 1471-4.
9. South Australian Cancer Registry. Epidemiology of cancer in South Australia. Incidence, mortality and survival 1977 to 1999. Incidence and mortality 1999. Adelaide: Department of Human Services, 2000.
10. Esteban D, Whelan S, Laudico A, Parkin DM (eds). Manual for Cancer Registry Personnel. IARC Technical Report No. 10. Lyon: International Agency for Research on Cancer (IARC), 1995.
11. SA NT DataLink 2019, Privacy Protecting Model. University of South Australia, Australia. Available: https://www.santdatalink.org.au/ [Accessed 5 October 2019].
12. Australian Government. National Statistical Service. A guide for data integration projects involving Commonwealth Data for Statistical and Research Purposes: The separation principle. Canberra: Australian Government, 2018. Available: https://statistical-data-integration.govspace.gov.au/topics/applying-the-separation-principle [Accessed 21 October 2019].
13. Tervonen HE, Aranda S, Roder D, et al. Cancer survival disparities worsening by socio-economic disadvantage over the last three decades in New South Wales, Australia. *BMC Public Health* 2017; 17(1): 691.
14. Australia Bureau of Statistics. Standard Australian Classification of Countries (SACC). ABS Catalogue No. 1269.0. ABS: Canberra. 2017. Available: https://www.ausstats.abs.gov.au/ausstats/subscriber.nsf/0/9A9C459F46EF3076CA25744B0015610A/$File/12690_Second%20Edition.pdf [Accessed 20 October 2019]
15. Australia Bureau of Statistics. Information Paper: an introduction to Socio-Economic Indexes for Areas (SEIFA) 2006. ABS Catalogue No. 2039.0. ABS: Canberra, 2017. Available: https://www.ausstats.abs.gov.au/ausstats/subscriber.nsf/0/D729075E079F9FDECA2574170011B088/$File/20390_2006.pdf [Accessed 20 October 2019].
16. Australia Bureau of Statistics. Australian Standard Geographical Classification (ASGC) Remoteness Area Correspondences, 2006. ABS Catalogue No.1216.0.15.003. ABS: Canberra, 2011. Available: https://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/1216.0.15.0032006?OpenDocument [Accessed 20 October 2019].
17. Armitage P, Berry G, Matthews JNS. Statistical methods in medical research (2nd Edition). Oxford, UK: Blackwell Scientific Publications, 1987.
18. StataCorp. Stata statistical software. Release 16. College Station, TX: StataCorp L.P., 2018.

19. Fine JP, Gray RJ. A proportional hazards model for subdistribution of a competing risk. *J Royal Stat Assoc* 1999; 94(446): 496-509.
20. Australian Institute of Health and Welfare. National cancer screening programs participation data. Canberra: AIHW, 2019.
21. Australian Institute of Health and Welfare. BreastScreen Australia monitoring report 2011–2012. Cancer series no. 86. Cat. no. CAN 83. Canberra: AIHW, 2014.
22. Tesarova P. Specific aspects of breast cancer therapy of elderly women. *Biomedical Research International* 2016; 1381695.
23. Australian Government. Department of Health and Ageing. BreastScreen Australia Evaluation. Evaluation Final Report. Canberra: Commonwealth of Australia, 2009.
24. Lauby-Secretan B, Scoccianti C, Loomis D, et al. Breast-cancer screening - viewpoint of the IARC Working Group. *New England Journal of Medicine* 2015; 372(24):2353-8.

**Table 1. Patient characteristics by TNM cancer stage; invasive breast cancers diagnosed in South Australia, 2000-2014***

| | I (n=6718) | II (n=5777) | III (n=1708) | IV (n=556) | Total (n=14759) | P |
|---|---|---|---|---|---|---|
| **Mean Age (year) (SD):** | 61.0 (12.2) | 60.0 (13.9) | 59.0 (14.3%) | 65.3 (15.2) | 60.6 (13.3) | <0.001 |
| **Age group:** | | | | | | <0.001 |
| <50 | 1143 (17.0%) | 1436 (24.9%) | 486 (28.5%) | 101 (18.2%) | 3166 (21.5%) | |
| 50-59 | 1877 (27.9%) | 1493 (25.8%) | 429 (25.1%) | 103 (18.5%) | 3902 (26.4%) | |
| 60-69 | 2121 (31.6%) | 1344 (23.3%) | 363 (21.3%) | 112 (20.1%) | 3940 (26.7%) | |
| 70-79 | 1072 (16.0%) | 929 (16.1%) | 267 (15.6%) | 124 (22.3%) | 2392 (16.2%) | |
| 80+ | 505 (7.5%) | 575 (10.0%) | 163 (9.5%) | 116 (20.9%) | 1359 (9.2%) | |
| **Country of birth:** | | | | | | 0.002 |
| Australia | 4101 (61.0%) | 3450 (59.7%) | 1035 (60.6%) | 332 (59.7%) | 8918 (60.4%) | |
| Other English-speaking countries | 985 (14.7%) | 858 (14.9%) | 226 (13.2%) | 75 (13.5%) | 2144 (14.5%) | |
| Non-English-speaking countries | 700 (10.4%) | 715 (12.4%) | 211 (12.4%) | 69 (12.4%) | 1695 (11.5%) | |
| Unknown | 932 (13.9%) | 745 (13.1%) | 236 (13.8%) | 80 (14.4%) | 2002 (13.6%) | |
| **SEIFA IRSD quintile:** | | | | | | <0.001 |
| 1 (most disadvantaged) | 1057 (15.7%) | 1063 (18.4%) | 319 (18.7%) | 131 (23.6%) | 2570 (17.4%) | |
| 2 | 1404 (20.9%) | 1126 (19.5%) | 332 (19.4%) | 125 (22.5%) | 2987 (20.2%) | |
| 3 | 1342 (20.0%) | 1165 (20.2%) | 355 (20.8%) | 112 (20.1%) | 2974 (20.2%) | |
| 4 | 1342 (20.0%) | 1168 (20.2%) | 341 (20.0%) | 88 (15.8%) | 2939 (19.9%) | |
| 5 (least disadvantaged) | 1572 (23.4%) | 1254 (21.7%) | 361 (21.1%) | 100 (18.0%) | 3287 (22.3%) | |
| **Remoteness:** | | | | | | 0.310 |
| Major city | 4978 (74.1%) | 4293 (74.3%) | 1290 (75.5%) | 418 (75.2%) | 10979 (74.4%) | |
| Inner regional | 760 (11.3%) | 651 (11.3%) | 186 (10.9%) | 57 (10.3%) | 1654 (11.2%) | |
| Outer regional | 783 (11.7%) | 653 (11.3%) | 193 (11.3%) | 64 (11.5%) | 1693 (11.5%) | |
| Remote | 162 (2.4%) | 141 (2.4%) | 32 (1.9%) | 13 (2.3%) | 348 (2.4%) | |
| Very remote | 34 (0.5%) | 39 (0.7%) | 7 (0.4%) | 4 (0.7%) | 84 (0.6%) | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Unknown | 1 (0.01%) | 0 | 0 | 0 | 1 (0.01%) | |
| **Diagnosis period:** | | | | | | 0.346 |
| 2000-2004 | 2022 (30.1%) | 1889 (32.7%) | 452 (26.5%) | 197 (35.4%) | 4560 (30.9%) | |
| 2005-2009 | 2368 (35.3%) | 1881 (32.6%) | 630 (36.9%) | 223 (40.1%) | 5102 (34.6%) | |
| 2010-2014 | 2328 (34.7%) | 2007 (34.7%) | 626 (36.7%) | 136 (24.5%) | 5097 (34.5%) | |
| **Vital status:** | | | | | | <0.001 |
| Died | 720 (10.7%) | 1186 (20.5%) | 582 (34.1%) | 436 (78.4%) | 2924 (19.8%) | |
| Alive | 5998 (89.3%) | 4591 (79.4%) | 1126 (65.9%) | 120 (21.6%) | 11835 (80.2%) | |
| **Cause of death:** | | | | | | <0.001 |
| Breast cancer | 209 (29.0%) | 680 (57.3%) | 460 (79.0%) | 391 (89.7%) | 1740 (59.5%) | |
| Other cancers | 170 (23.6%) | 136 (11.5%) | 42 (7.2%) | 19 (4.4%) | 367 (12.6%) | |
| Non-cancer | 341 (47.6%) | 370 (31.2%) | 80 (13.8%) | 26 (6.0%) | 817 (27.9%) | |

*P from one-way ANOVA for age in years and Chi-square test for others.

Vital status and cause of death from cancer registry, censoring on 31th Dec 2014.

SD: Standard deviation; SEIFA: Socioeconomic Index for Areas; IRSD: Index of Relative Socio-economic Disadvantage.

**Table 2: Odds ratios (95% confidence intervals) for diagnosis with advanced (TNM III or IV) as opposed to more localized (TNM I or II) breast cancers diagnosed in 2000-2014 in South Australia* (N=14759)**

| Characteristic | Case numbers - advanced/all stages | Odds ratio for advanced stage (unadjusted) | Odds ratio for advanced stage** (adjusted) |
|---|---|---|---|
| **Age at diagnosis (years):** | | | |
| <50 | 587/3166 | 1.00 | 1.00 |
| 50-59 | 532/3902 | 0.69 (0.61-0.79) | 0.70 (0.62-0.80) |
| 60-69 | 475/3940 | 0.60 (0.53-0.69) | 0.60 (0.53-0.69) |
| 70-79 | 391/2392 | 0.86 (0.75-0.99) | 0.85 (0.74-0.98) |
| 80+ | 279/1359 | 1.13 (0.98-1.33) | 1.11 (0.95-1.31) |
| **Country of birth:** | | | |
| Australia | 1370/8918 | 1.00 | 1.00 |
| Other English-speaking countries | 301/2144 | 0.90 (0.79-1.03) | 0.91 (0.80-1.04) |
| Non-English-speaking countries | 280/1695 | 1.09 (0.95-1.26) | 1.08 (0.93-1.24) |
| Unknown | 316/2002 | 1.04 (0.91-1.18) | 1.02 (0.89-1.16) |
| **Diagnostic period:** | | | |
| 2000-2004 | 649/4560 | 1.00 | 1.00 |
| 2005-2009 | 853/5102 | 1.21 (1.08-1.35) | 1.20 (1.07-1.34) |
| 2010-2014 | 762/5097 | 1.06 (0.95-1.19) | 1.06 (0.95-1.19) |
| **Residential remoteness:** | | | |
| Major city | 1078/10979 | 1.00 | 1.0 |
| Inner regional | 243/1654 | 0.93 (0.81-1.08) | 0.96 (0.82-1.11) |
| Outer region/remote/very remote | 313/2126 | 0.94 (0.82-1.07) | 0.88 (0.77-1.02) |
| **SEIFA IRSD quintile:** | | | |
| 1 (most disadvantaged) | 450/2570 | 1.00 | 1.00 |
| 2 | 457/2987 | 0.85 (0.74-0.98) | 0.87 (0.75-1.00) |
| 3 | 467/2974 | 0.88 (0.76-1.01) | 0.88 (0.76-1.01) |
| 4 | 429/2939 | 0.81 (0.70-0.93) | 0.79 (0.68-0.92) |
| 5 (least disadvantaged) | 461/3287 | 0.77 (0.67-0.89) | 0.75 (0.65-0.87) |

*Adjusted ROs from logistic regression model including age, country of birth, diagnosis period, SES quintile, and residential area

SEIFA: Socioeconomic Index for Areas; IRSD: Index of Relative Socio-economic Disadvantage.

**Table 3: Sub-hazard ratios (95% confidence intervals) for breast cancer-specific mortality in South Australia during 2000-2014 (N=14759)**

| Characteristic | Breast cancer death/death | Unadjusted SHR* | Adjusted SHR** |
|---|---|---|---|
| **TNM stage:** | | | |
| I | 209/720 | 1.00 | 1.00 |
| II | 680/1186 | 3.99 (3.42-4.65) | 3.87 (3.32-4.53) |
| II | 460/582 | 10.69 (9.09-12.57) | 10.87 (9.22-12.81) |
| IV | 391/436 | 45.82 (38.15-55.03) | 41.97 (34.78-50.65) |
| **Age at diagnosis (years):** | | | |
| <50 | 365/405 | 1.00 | 1.00 |
| 50-59 | 404/526 | 0.83 (0.77-1.02) | 1.10 (0.95-1.27) |
| 60-69 | 342/556 | 0.78 (0.68-0.90) | 1.05 (0.91-1.22) |
| 70-79 | 329/699 | 1.31 (1.13-1.52) | 1.43 (1.22-1.67) |
| 80+ | 300/738 | 2.22 (1.89-2.59) | 2.24 (1.90-2.66) |
| **Country of birth:** | | | |
| Australia | 1049/1777 | 1.00 | 1.00 |
| Other English-speaking countries | 247/412 | 0.98 (0.85-1.12) | 1.01 (0.87-1.17) |
| Non-English-speaking countries | 200/346 | 1.02 (0.87-1.18) | 0.98 (0.84-1.15) |
| Unknown | 244/389 | 1.08 (0.94-1.25) | 1.15 (1.00-1.33) |
| **Diagnostic period:** | | | |
| 2000-2004 | 884/1512 | 1.00 | 1.00 |
| 2005-2009 | 654/1076 | 0.81 (0.73-0.90) | 0.75 (0.67-0.83) |
| 2010-2015 | 202/336 | 0.62 (0.53-0.72) | 0.57 (0.48-0.67) |
| **Residential remoteness:** | | | |
| Major city | 1302/2186 | 1.00 | 1.00 |
| Inner regional | 185/313 | 0.99 (0.85-1.16) | 1.01 (0.86-1.20) |
| Outer regional/remote/very remote | 253/425 | 1.01 (0.88-1.15) | 0.97 (0.84-1.13) |
| **SEIFA IRSD quintile:** | | | |
| 1 (most disadvantaged) | 364/605 | 1.00 | 1.00 |
| 2 | 371/604 | 0.88 (0.76-1.02) | 0.93 (0.79-1.09) |
| 3 | 353/613 | 0.80 (0.69-0.93) | 0.85 (0.72-0.99) |
| 4 | 328/544 | 0.79 (0.68-0.92) | 0.85 (0.73-1.00) |
| 5 (least disadvantage) | 324/558 | 0.67 (0.58-0.78) | 0.73 (0.62-0.87) |

*Unadjusted SHRs derived from univariate competing risk regression modelling, deaths followed to December 31, 2014.
**Adjusted SHRs derived from multivariate competing risk regression model adjusting by including cancer stage, age, country of birth, diagnosis period, residential remoteness and SEIFA quintile.
SHR: Sub-hazard ratio; SEIFA: Socioeconomic Index for Areas; IRSD: Index of Relative Socio-economic Disadvantage.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

| | Item No | Recommendation | Page No |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 4 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 2 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 4,5 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 4,5 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 2,4,5 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 5,6 |
| 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 | 4,5 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 10 |
| Study size | 10 | Explain how the study size was arrived at | 4,5,6 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 5 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 6 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 6 |
| | | (*c*) Explain how missing data were addressed | 5,6 |
| | | (*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 | 14,16,17 |
| | | (b) Give reasons for non-participation at each stage | N/A |
| | | (c) Consider use of a flow diagram | N/A |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 14-17 |
| | | (b) Indicate number of participants with missing data for each variable of interest | 14-17 |
| | | (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 | 14-17 |

| | | | |
|---|---|---|---|
| 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<br>(*b*) Report category boundaries when continuous variables were categorized<br>(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | 6-10 & 14-17<br>14-17<br>N/A |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 6-10 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 7-10 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 2, 10 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 7-10 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 7-10 |
| **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 | 11 |

*Give information separately for exposed and unexposed groups.

**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 http://www.strobe-statement.org.

BMJ Open

# Monitoring TNM stage of female breast cancer and survival across the South Australian population, with national and international TNM benchmarking

| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2020-037069.R1 |
| Article Type: | Original research |
| Date Submitted by the Author: | 25-Mar-2020 |
| Complete List of Authors: | Li, Ming; University of South Australia, Cancer Research Institute<br>Roder, David; University of South Australia, Cancer Research Institute; Cancer Institute NSW<br>D'Onise, Katina; SA Health Department for Health and Wellbeing, Prevention and Population Health<br>Walters, David; The Queen Elizabeth Hospital, Department of Surgery; The University of Adelaide, Faculty of Health and Medical Sciences<br>Farshid, Gelareh; SA Pathology; The University of Adelaide, Faculty of Health and Medical Sciences<br>Buckley, Elizabeth; University of South Australia, Cancer Research Institute<br>Karapetis, Chris; Flinders University, Medical Oncology<br>Joshi, Rohit; The University of Adelaide, Faculty of Health and Medical Sciences; Adelaide Oncology and Haematology, Cancer Research and Clinical Trials<br>Price, Timothy ; The University of Adelaide, Faculty of Health and Medical Sciences; The Queen Elizabeth Hospital, Clinical Cancer Research<br>Townsend, Amanda; The Queen Elizabeth Hospital, Clinical Cancer Research; Basil Hetzel Institute for Translational Health Research<br>Miller, Caroline; South Australian Health and Medical Research Institute, Health Policy Centre; The University of Adelaide, Faculty of Health and Medical Sciences<br>Currow, David; Cancer Institute NSW<br>Powell, Kate; South Australian Health and Medical Research Institute, Health Policy Centre; SA Health Department for Health and Wellbeing, SA Clinical Cancer Registry<br>Buranyi-Trevarton, Dianne; SA Health Department for Health and Wellbeing, SA Clinical Cancer Registry<br>Olver, Ian; The University of Adelaide, Faculty of Health and Medical Sciences |
| Primary Subject Heading: | Public health |
| Secondary Subject Heading: | Epidemiology, Health services research, Oncology |
| Keywords: | Breast tumours < ONCOLOGY, Epidemiology < ONCOLOGY, PUBLIC HEALTH |

*I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.*

*The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.*

*Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.*

# Monitoring TNM stage of female breast cancer and survival across the South Australian population, with national and international TNM benchmarking

Ming Li[1], David Roder[1, 11]*, Katina D'Onise[2], David Walters[3, 7], Gelareh Farshid[4, 7], Elizabeth Buckley[1], Chris Karapetis[5], Rohit Joshi[6, 7], Timothy Price[7, 8], Amanda Townsend[8, 9], Caroline Miller[7, 10], David Currow[11], Kate Powell[10, 12], Dianne Buranyi-Trevarton[12], Ian Olver[7]

[1] Cancer Research Institute, University of South Australia, Adelaide, South Australia, Australia

[2] Prevention and Population Health, SA Health Department for Health and Wellbeing, Adelaide, South Australia, Australia

3 Department of Surgery, Queen Elizabeth Hospital, Woodville South, South Australia, Australia

4 SA Pathology, Adelaide, South Australia, Australia

5 Medical Oncology, Flinders University, Bedford Park, South Australia, Australia

6 Cancer Research and Clinical Trials, Adelaide Oncology and Haematology, North Adelaide, South Australia, Australia

7 Faculty of Health and Medical Sciences, University of Adelaide, Adelaide, South Australia, Australia

8 Clinical Cancer Research, Queen Elizabeth Hospital, Woodville South, South Australia, Australia

9 Basil Hetzel Institute for Translational Health Research, Woodville South, South Australia, Australia

10 Health Policy Centre, South Australian Health & Medical Research Institute (SAHMRI), Adelaide, South Australia, Australia

11 Cancer Institute NSW, Eveleigh, New South Wales, Australia

12 SA Clinical Cancer Registry, South Australian Department for Health and Wellbeing, Adelaide, South Australia, Australia

*** Corresponding author:** David Roder

Mobile: 0478 408 386

Office: 08 8302 2640

Email: David.roder@unisa.edu.au

Postal address:

University of South Australia

Cancer Research Institute (CWE-48)

GPO Box 2471

Adelaide SA 5001

**Abstract:**

**Objective:** Using linked cancer registry and administrative data to monitor Tumour, Node and Metastases (TNM) stage and survival from female breast cancer in Australia.

**Method:** Analysis of 2000-2014 diagnoses with linked population-based data to investigate: (1) sociodemographic predictors of advanced stage (stages III & IV), using unadjusted and adjusted logistic regression; and (2) sociodemographic factors and stage as predictors of breast-cancer survival using competing risk regression.

**Design:** Population-based registry cohort

**Setting and participants:** 14759 South Australian women diagnosed in 2000-2014

**Primary and secondary outcome measures:** Stage and survival

**Results:** At diagnosis, 46% of women were classified as stage I, 39% as stage II, 12% as stage III, and 4% as stage IV. After adjusting for sociodemographic factors, advanced stage was more common: (a) for ages <50 years; and although not statistically significant, for ages 80+ years; and (b) in women from socioeconomically disadvantaged areas. Compared with 2000-2004 diagnoses, stage and sociodemographic adjusted risks (sub-hazard ratios - SHR) of breast cancer death were lower in 2005-2009 (SHR: 0.75, 95% CI: 0.67-0.83) and 2010-2015 (SHR: 0.57, 95% CI: 0.48-0.67). Compared with stage I, the SHR was 3.87 (95% CI: 3.32-4.53) for stage II, 10.87 (95% CI: 9.22-12.81) for stage III, and 41.97 (95% CI: 34.78-50.65) for stage IV. Women aged 70+ years at diagnosis and those living in the most socioeconomically disadvantaged areas were at elevated risk of breast cancer death, independent of stage and sociodemographic factors.

**Conclusions:** Stage varied by age, diagnostic period, and socioeconomic status, and was a stronger predictor of survival than other statistically significant sociodemographic predictors. Achieving earlier diagnosis outside the original BreastScreen target of 50-69 years (as applying <2014) and in residents of socioeconomically disadvantaged areas likely would increase cancer survival at a population level.

**Key words:** breast tumours; epidemiology; public health

**Word Count:** Abstract – 288; Main text – 2992

**Article Summary:**

**Strengths and Limitations**

Strengths:

- Shows the utility of readily available registry and administrative data for population-based monitoring of TNM stage
- Shows the face validity of these TNM stage distributions through comparisons with data from special studies and international benchmarks
- Shows plausible predictive effects of stage on survival

Limitations:

- Study limited to broad TNM categories due to limited detail available
- Use of AJCC 7th Revision with further adaptation required for the 8th Revision

**Introduction:**

Breast cancer is the most common cancer recorded in Australian women by population registries (1). The 5-year relative survival from female breast cancer increased markedly from 72% in 1984-1988 to 91% in 2011-2015 (1). This was attributed mostly to treatment advances and earlier cancer detection through the national population screening program established in 1991 (1, 2). The screening program offered 2-yearly screening mammograms to women in the target age of 50-69 years, extending to 74 years from 2014 (1, 2). Approximately 54% of women in the target age range participate during a two-year period. Women aged 40-49 years, particularly women with a strong family history and those older than the screening target, are eligible for screening but not actively invited (1, 2).

Anatomic stage of cancer is a key predictor of cancer survival (3, 4). The Tumour, Node and Metastases (TNM) staging system is a gold standard for staging most solid cancers in clinical practice and can be used, with minor modification, to monitor stage at a population level through cancer registries (5). TNM stage was recorded by population registries for 95% of female breast cancers diagnosed in Australia in a one-off study in 2011 (5). This followed an earlier pathfinder study for methodological development (6). Staging data are useful to service planners as indicators of need, to assess alignment of care with recommendations, to evaluate survival, to design interventions to address disparities, and to evaluate population impact of new therapies by stage.

We use linked registry and administrative data for 14759 South Australian women diagnosed with invasive breast cancer in 2000-2014 to investigate: (1) sociodemographic predictors of advanced TNM stage; and (2) TNM stage as a predictor of breast cancer survival.

**Methods:**

*Study design*

Two historic cohort designs were used. The predictor variables for stage as the outcome in the first analysis were sociodemographic characteristics (i.e., age at diagnosis, country of birth, residential area socioeconomic disadvantage and remoteness, and diagnostic period), and for survival as the outcome in the second analysis, TNM stage and these sociodemographic variables.

*Deriving stage*

TNM stage was recorded for 96% of women with breast cancers diagnosed in 2000-2014, using pathology and hospital reporting. The stage distribution was checked with aggregated statistical profiles from the Breast Quality Audit of Breast Surgeons of Australia and New Zealand (7). For consistency, staging processes followed national guidelines developed for population-based registries and used in a 2011 national study (5, 6).

Breast tumour diameters and nodal status were obtained for assessing stage through the South Australian Cancer Registry (SACR) and distant metastases were indicated by inpatient diagnosis codes. SA Clinical Cancer Registry data for major public hospitals were used for validity checking and to fill gaps. Receptor status and other biomarkers were not addressed as they were not routinely recorded by registries throughout the study period and not included in the national TNM staging protocol developed for population-wide monitoring (5).

Stage was broadly classified as stage I, II, III or IV, according to criteria of the American Joint Committee on Cancer (AJCC, 7th Revision), to reduce inconsistencies from changes in AJCC revisions (8).

*Data sources*

Population-based invasive breast cancer data (ICD-O-3 C50) were obtained from the SACR. Operations of the SACR have been described previously (9). All invasive breast cancers diagnosed in South Australia were included and coded using international registry standards (9, 10). Reporting by pathology laboratories and hospitals is a legal requirement (9).

For each cancer, SACR records the primary site, morphology, diagnosis date, and the woman's country of birth, death date and cause, and postcode-derived relative socioeconomic disadvantage and geographic remoteness (9). The Registry of Births, Deaths and Marriages and National Death Index (NDI) are used as sources of death data, with causes coded to cancer type or non-cancer (9).

Linkage of SACR and hospital inpatient data was predominantly through South Australia Northern Territory DataLink using name, sex, date of birth and address for matching (11, 12). Patient identifiers were separated from clinical content to protect privacy (12). The process comprised: (1) After record de-duplication, deterministic matching to a Master Linkage File built from extracts of over 60 data sources, achieving 97% deterministic matching of inpatient and SACR data; (2) Non-exact matches then linked through probabilistic means; (3) Uncertain matches clerically reviewed for final determination.

*Other variables*

Age at diagnosis was classified as: <50, 50-59, 60-69, 70-79 or 80+ years; and country of birth as Australia, other predominantly English-speaking country or predominantly non-English speaking country, as previously (13, 14). Socioeconomic status was derived from residential postcode at diagnosis using the Socioeconomic Index for Areas (SEIFA) Index of Relative Socioeconomic Disadvantage (IRSD) expressed in quintiles (15). Residential area was classified as a major city, inner regional, outer regional, remote or very remote area, using the Australian Standard Geographical Classification (ASGC) Remoteness index (16). Diagnostic period was categorized as 2000–2004, 2005–2009, and 2010–2014.

*Statistical analysis*

TNM stage was analysed by population characteristic using analysis of variance (ANOVA) for age and conventional chi-square or ranked tests depending on variable distributions (17, 18). Advanced stage (III or IV) as opposed to early stage (I or II) was analysed by sociodemographic descriptors using unadjusted and adjusted logistic regression (17, 18).

Deaths were classified as due to breast cancer, as compared with another cause, and predictors of survival from breast cancer were analysed for period from diagnosis to death or until December 31st, 2014, whichever came first. Predictors of breast cancer death were investigated using competing risk regression models (Stata module "stcrreg") (18, 19), regarding deaths from causes other than breast cancer as the competing risk. Predictors were adjusted for stage and sociodemographic characteristics.

Stata 14 (StataCorp, College Station, Texas, USA) was used, with statistical significance set at $p<0.05$. All survival analyses used complete case data.

**Results:**

*Population description:*

The mean age of the 14759 staged cases was 61 years, with 53% aged 50-69 years (Table 1). For women of known country of birth, 70% were born in Australia, 17% in other predominantly English-speaking countries, and 13% in predominantly non-English-speaking countries. SACR data indicated that 30% of the cohort were born outside of Australia. Of these, 50% were born in the United Kingdom/Ireland, 21% in Southern or Eastern Europe, 11% in Western Europe, 9% in Asia, and 9% elsewhere. Almost three quarters (74%) resided in a major city, 11% in inner regional locations, and 14% in outer regional, remote or very remote areas. The percentage by residential socioeconomic disadvantage ranged from 17% for the most disadvantaged to 22% for the least disadvantaged quintile. The percentage by diagnostic period increased from 31% for 2000-2004 to 35% for 2005-2009 and 2010-2014.

*Cancer stage:*

The TNM stage distribution was: stage I, 46%; stage II, 39%; stage III, 12%; and stage IV, 4%. Differences in stage were found in unadjusted analysis by age ($p<0.001$), country of birth ($p=0.002$), and SEIFA disadvantage ($p<0.001$), but not by residential remoteness ($p=0.310$) or diagnostic period ($p=0.346$) (Table 1).

Compared with women aged <50 years at diagnosis, the adjusted odds ratio (OR) for advanced stage was: 0.70 (95% CI 0.62-0.80) for ages 50-59 years, 0.60 (95% CI 0.53-0.69) for 60-69 years, and 0.85 (95% CI 0.74-0.98) for 70-79 years. Higher adjusted risks of advanced stage tended occur in ages <50

years and 80+ years, although the difference for ages 80+ years compared with <50 years did not achieve statistical significance (OR: 1.11 95% CI: 0.95-1.31) (Table 2).

Adjusted odds ratios for advanced cancer were lower among women of least residential socioeconomic disadvantage (Q4/Q5) than most disadvantage (Q1) (OR 0.79 95% CI 0.68-0.92) for Q4 and OR 0.75 (95% CI: 0.65-0.87) for Q5 (least disadvantage). Risk of advanced stage did not differ in adjusted analyses by country of birth or residential remoteness (Table 2).

While the adjusted odds ratio for advanced cancer was higher in 2005-2009 than the 2000-04 baseline (OR 1.20 95% CI: 1.07-1.34), the difference between 2010-14 and 2000-04 was not significant (OR 1.06 95% CI: 0.95-1.19).

Analyses by age showed heterogeneity for advanced stage by diagnostic period. During 2000-2004, women aged 80+ years were significantly more likely to have advanced stage than the reference age (<50 years) (OR 1.50 95% CI: 1.12-2.01) but significant corresponding associations were not observed in 2005-2009 (OR 1.16 95% CI: 0.90-1.50) or 2010-2014 (OR 0.82 95% CI: 0.62-1.10).

Supplementary analysis: When the analysis was repeated sub-classifying age <50 years as <40 and 40-49 years, adjusted odds ratios for advanced stage were essentially unchanged for sociodemographic factors. Compared with <40 years, the adjusted odds ratios were: 0.79 (0.64-0.97) for 40-49 years; 0.59 (0.48-0.72) for 50-59 years; 0.50 (0.41-0.62) for 60-69 years; 0.71 (0.58-0.88) for 70-79 years; and 0.93 (0.75-1.16) for 80+ years.

*Breast cancer mortality:*

Of the 14759 women, 2924 (19.8%) had died from any cause and 1740 (11.8%) from breast cancer by the end of the study (Table 1). Adjusted sub-hazard ratios (Table 3) varied by: (1) stage – increasing with more advanced stage to 41.97 (95% CI 34.78-50.65) for stage IV compared with stage 1; (2) age at diagnosis – increasing with age to 2.24 (95% CI 1.88-2.66) for age 80+ compared with <50 years; and (3) residential socioeconomic disadvantage – reducing to 0.73 (95% CI 0.62-0.87) for the least compared with most disadvantaged quintile. The adjusted risk of breast cancer death reduced, independently of stage and sociodemographic factors, in the later diagnostic periods compared with the 2000-2004 reference (SHR 0.75 95% CI: 0.67-0.83) for 2005-2009 and 0.57 (95% CI 0.48-0.67) for 2010-2014). Significant differences were not found in unadjusted or adjusted analyses by country of birth or residential remoteness.

Supplementary analysis: When the analysis was repeated sub-classifying age <50 years as <40 and 40-49 years, adjusted sub-hazards ratios were essentially the same as in the earlier analysis by other sociodemographic factors and stage. Compared with <40 years, the adjusted sub-hazards ratios were: 0.64 (0.52-0.80) for 40-49 years; 0.80 (0.65-0.97) for 50-59 years; 0.77 (0.62-0.94) for 60-69 years; 1.04 (0.84-1.28) for 70-79 years; and 1.63 (1.30-2.03) for 80+ years.

**Discussion:**

A very similar stage distribution was found for staged invasive female breast cancers in South Australia in 2000-2014 to that for the Australian national study for 2011 (5). This may reflect the common standards for screening, treatment, and accreditation, and similar although not identical screening participation (20-22).

Stage distributions were also similar in South Australia to distributions for staged breast cancers in Canada and England (5). The distributions in South Australia (2000-2014) compared with Australia (2011), Canada (2013) and England (2012) were: (1) stage I - 46% compared with 46%, 47% and 44% respectively; (2) stage II - 39% compared with 37%, 35% and 39% respectively; (3) stage III - 12% compared with 13%, 12% and 10% respectively; and (4) stage IV - 4% compared with 5%, 6% and 7% respectively (5) (Figure 1).

These differences appear minor and smaller than anticipated, given potential effects of methodological and geographic differences (5). The marginally higher proportion of early stage I and II of 85% for South Australia compared with 82% for Australia may also have been influenced by a marginally higher screening participation in South Australia (20, 21).

The proportion with advanced cancers (stage III or IV) was lower for ages 50-79 years than younger or older women. A similar pattern was seen for staged cancers in Australia (2011) where the age-standardized percentage with stages III or IV was 16% compared with 21% for younger and 25% for older women (5). This likely reflects targeting of women aged 50-69 years for screening in 2000-2013 and availability of screening on demand from 70 years during the study period (1, 2). In addition, women aged 80+ years, through a higher prevalence of frailty and comorbidity, may have been slower to access clinical services (5). Notably a higher odds ratio for advanced cancers presented in ages 80+ years than in younger women in 2000-2014, although this was less obvious for later diagnostic periods, especially 2010-2014, potentially reflecting a growing emphasis on early diagnosis in older women (22). Supplementary analysis showed a lower odds ratio for advanced cancer in women aged 40-49 than <40 years and in the 50-79-year age range, likely reflecting screening availability and potentially biological factors (1, 2).

Among women with breast cancer, the proportion by age ranged from 17% for the most disadvantaged quintile to 22% for the least disadvantaged, consistent with the Australia-wide gradient for 2010-2014 (5). Residents of the most disadvantaged quintile were at higher risk of advanced cancers than the least disadvantaged quintile in this study, which is confirmatory of the difference found nationally in 2011 (21% vs 16%) (5). Screening participation could have contributed, it being lower for disadvantaged than advantaged areas (5). Although screening services have introduced initiatives to address needs of women from disadvantaged areas, more research into barriers and opportunities would be desirable.

The absence of differences in risk of advanced stages in our study by residential remoteness may reflect the reach of mobile screening clinics in rural areas. Differences also appeared small in the national survey with 18% of staged cases having advanced cancers among major city residents compared with 17% for regional areas and 20% for remote and very remote areas (5). The absence of a difference in risk by country of birth in the present study is reassuring from an equity perspective.

Predictably the proportion of cases dying from breast cancer increased with TNM stage (from 3% for stage I to 70% for stage IV). Adjusted analyses confirmed stage to be the strongest predictor of survival. The National BreastScreen Evaluation Report of 2009, using data sourced from the Victorian Cancer Registry, indicated that the percentage of breast cancers with diameters ≤15mm was higher at 64% in women notified through BreastScreen than the 39% for other women in the 50-69-year age range, which likely contributed to the BreastScreen-related survival advantage (23). An Expert Panel from 16 countries assembled by the International Agency for Research on Cancer reported in 2015 that participation of women aged 50-69 years in mammography screening can reduce the risk of breast cancer death by approximately 40% (24). In addition, the national study showed a 5-year relative survival of 91% for 2011-2015 for all stages combined, but varying markedly by stage (i.e., >95% of women with stages TNM I and II survived five years compared with 81% for stage III and 32% for stage IV) (5).

Older age at diagnosis was predictive of lower survival in the present study, with the lowest survival applying to ages 80+ years. The national study provided consistent findings with the lowest 5-year relative survival of 81% applying to women aged 75+ years (5). Supplementary analysis with a finer age breakdown confirmed the lowest survival to apply to 80+ ages in the present study.

Socioeconomic status was also predictive with residents of the least disadvantaged areas having the highest survival. This is consistent with national data for 2006-2010 (5). Factors potentially responsible warrant further study and could include artificial effects of lead time and overdiagnosis, plus real effects due to differences in health literacy, variations in engagement with health protection, competing pressures on time and resources by level of disadvantage, and a tendency for lower screening participation in the most disadvantaged areas (5).

A major increase in survival outcomes was evident in more recent diagnostic periods, which is also seen in the national data where 5-year relative survival increased from 72% in 1984-1988 to 91% in 2010-2014 (5). This may reflect combination effects of artificial influences from differences in lead time and overdiagnosis, plus real benefits from screening and treatment advances, among them an increased use of specialized breast cancer centres and advances in adjuvant therapies (24). The more advanced breast-cancer stage distribution for South Australia in 2005-2009 was unexpected and warrants further investigation. These years represented the end of the film-reading era prior to transfer

to digital technology. Despite this peak in advanced cases, it is reassuring to see a steady secular increase in survival.

The present study follows the national study of stage (5). Stage was derived from pathology reporting and hospital reporting and stage distributions were checked with statistical profiles from the Quality Audit of Breast Surgeons of Australia and New Zealand (7). Results complement earlier data: from New South Wales, Australia, based on localised, regional and distant SEER Summary Stage, where a similar survival gradient was observed with higher stage for follow-up limited to ≤3 years from diagnosis (25, 26); and on breast cancer mortality trends for Australia which did not include data on stage or survival (27).

Limitations included restricting stage to four major categories to avoid inconsistencies due to changes at a more detailed level across versions of AJCC TNM coding. Further efforts are needed to improve accuracy of staging, although the 96% coverage of invasive cancers with staging was high and similar to coverage observed in other studies in Australia, Canada and England (5). Another limitation was lack of adjustment for post-diagnostic explanatory variables such as treatment practices, which may have affected sociodemographic survival differences. We plan to address these aspects in a further investigation of linked data.

Data on race and ancestry were not available for this study. While Indigenous status is recorded, numbers were too small for meaningful analysis. We therefore used country of birth as a crude marker of diversity according to whether predominantly English speaking. It is important with increasing ethnic diversity in Australia that greater attention be given to ethnic descriptors in health data collections.

**Conclusions:** Stage was a stronger predictor of survival outcome than sociodemographic predictors. Achieving earlier diagnosis outside the original screening target of 50-69 years and in residents of socioeconomically disadvantaged areas likely would further increase cancer survival at a population level. The present data show plausible stage distributions and effects on survival, using readily available data for staging. The uptake of voluntary screening from age of 40 years may improve outcomes for patients under 50 years and more targeted screening for patients with genetic risk and breast density may have positive impacts.

**Declarations:**

**Ethics approval and consent to participate:** Ethics approval for the study was obtained from research ethics committees of the South Australian Health Department (SA Health: HREC/17/SAH/38), University of South Australia (UNISA: 200021), and Australian Institute of Health and Welfare (AIHW: EO2017/3/361).

**Patient consent:** A Waiver of Consent was granted by the research ethics committees and Legal Authorization for data collection without consent was provided under the South Australian Health Care Act. Individual consent to participate was waived due to the absence of identifiers and contact details in the linked data, the size of the study, the need for close to complete participation to avoid statistical bias, and adherence to the separation of clinical data from identifiers to protect privacy. Only aggregated data are presented.

**Patient and Public Involvement (PPI):** We did not directly include PPI in this study, but the database used in the study was developed with PPI and is updated by a committee that includes patient representatives.

**Competing Interests:** Dr. Roder reports grants from National Breast Cancer Foundation, grants from Cancer Council SA, during the conduct of the study.

**Availability of data and materials:** The data used in this study are available from the South Australian Department for Health and Wellbeing (South Australian Cancer Registry & Integrated South Australian Activity Collection). Source data only would be publicly available with the approval of these source data custodians.

**Funding:** This project is supported by a grant from the National Breast Cancer Foundation (CRP-17-001), the Cancer Council's Beat Cancer Project on behalf of its donors, and the State Government through the Department of Health.

**Author contributions:** Study concept: DR, ML; Study Design: DR, ML; Data acquisition: DR, DBT, KP; KDO; Data Analysis: ML, DR; Data interpretation: ML, DR, DBT, KP, IO, GF; Manuscript writing: ML, DR; Review of manuscript: ML, DR, KDO, DW, GF, EB, CK, RJ, TP, AT, CM, DC, KP, DBT, IO; All authors read and approved the final version.

**Acknowledgements:** We are grateful to the National Breast Cancer Foundation, the SA Government, Cancer Council South Australia, the Breast Surgeons of Australia and New Zealand and SANT DataLink for their support.

**References:**

1. Australian Institute of Health and Welfare. Cancer in Australia 2019. Cancer series no.119. Cat. no. CAN 123. Canberra: AIHW, 2019.
2. Australian Government, Department of Health. Expansion of BreastScreen Australia. Canberra: Commonwealth of Australia, 2019.
3. McPhail S, Johnson S, Greenberg D, et al. Stage at diagnosis and early mortality from cancer in England. British Journal of Cancer. 2015;112 Suppl 1:S108-15.

4. de Mello Ramirez Medina J, de Araujo Trugilho I, Mendes GNB, et al. Advanced clinical stage at diagnosis of breast cancer is associated with poorer health-related quality of life: a cross-sectional study. European Journal of Breast Health 2019;15(1): 26-31.
5. Cancer Australia. National Cancer Control Indicators. Sydney: Cancer Australia, 2019. Available: https://ncci.canceraustralia.gov.au/ [Accessed 1 October 2019].
6. National Breast and Ovarian Cancer Centre. Breast cancer staging and treatment: Data linkage report. National Breast and Ovarian Cancer Centre, Surry Hills, NSW, 2010.
7. Royal Australasian College of Surgeons (RACS). BreastSurgANZ quality audit. Adelaide: RACS, 2019. Available: https://www.surgeons.org/research-audit/morbidity-audits/morbidity-audits-managed-by-racs/breastsurganz-quality-audit [Accessed 10 October 2019].
8. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and future TNM. Annals of Surgical Oncology 2010; 17(6): 1471-4.
9. South Australian Cancer Registry. Epidemiology of cancer in South Australia. Incidence, mortality and survival 1977 to 1999. Incidence and mortality 1999. Adelaide: Department of Human Services, 2000.
10. Esteban D, Whelan S, Laudico A, Parkin DM (eds). Manual for Cancer Registry Personnel. IARC Technical Report No. 10. Lyon: International Agency for Research on Cancer (IARC), 1995.
11. SA NT DataLink 2019, Privacy Protecting Model. University of South Australia, Australia. Available: https://www.santdatalink.org.au/ [Accessed 5 October 2019].
12. Australian Government. National Statistical Service. A guide for data integration projects involving Commonwealth Data for Statistical and Research Purposes: The separation principle. Canberra: Australian Government, 2018. Available: https://statistical-data-integration.govspace.gov.au/topics/applying-the-separation-principle [Accessed 21 October 2019].
13. Tervonen HE, Aranda S, Roder D, et al. Cancer survival disparities worsening by socio-economic disadvantage over the last three decades in New South Wales, Australia. *BMC Public Health* 2017; 17(1): 691.
14. Australia Bureau of Statistics. Standard Australian Classification of Countries (SACC). ABS Catalogue No. 1269.0. ABS: Canberra. 2017. Available: https://www.ausstats.abs.gov.au/ausstats/subscriber.nsf/0/9A9C459F46EF3076CA25744B0015610A/$File/12690_Second%20Edition.pdf [Accessed 20 October 2019]
15. Australia Bureau of Statistics. Information Paper: an introduction to Socio-Economic Indexes for Areas (SEIFA) 2006. ABS Catalogue No. 2039.0. ABS: Canberra, 2017. Available: https://www.ausstats.abs.gov.au/ausstats/subscriber.nsf/0/D729075E079F9FDECA2574170011B088/$File/20390_2006.pdf [Accessed 20 October 2019].
16. Australia Bureau of Statistics. Australian Standard Geographical Classification (ASGC) Remoteness Area Correspondences, 2006. ABS Catalogue No.1216.0.15.003. ABS: Canberra,

2011. Available: https://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/1216.0.15.0032006?OpenDocument [Accessed 20 October 2019].

17. Armitage P, Berry G, Matthews JNS. Statistical methods in medical research (2nd Edition). Oxford, UK: Blackwell Scientific Publications, 1987.
18. StataCorp. Stata statistical software. Release 16. College Station, TX: StataCorp L.P., 2018.
19. Fine JP, Gray RJ. A proportional hazards model for subdistribution of a competing risk. *J Royal Stat Assoc* 1999; 94(446): 496-509.
20. Australian Institute of Health and Welfare. National cancer screening programs participation data. Canberra: AIHW, 2019.
21. Australian Institute of Health and Welfare. BreastScreen Australia monitoring report 2011–2012. Cancer series no. 86. Cat. no. CAN 83. Canberra: AIHW, 2014.
22. Tesarova P. Specific aspects of breast cancer therapy of elderly women. *Biomedical Research International* 2016; 1381695.
23. Australian Government. Department of Health and Ageing. BreastScreen Australia Evaluation. Evaluation Final Report. Canberra: Commonwealth of Australia, 2009.
24. Lauby-Secretan B, Scoccianti C, Loomis D, et al. Breast-cancer screening - viewpoint of the IARC Working Group. *New England Journal of Medicine* 2015; 372(24):2353-8.
25. Walters S, Maringe C, Butler J, et al. The ICBP Module 1 Working Group20. Breast cancer survival and stager at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK, 2000-2007: a population-based study. *Brit J Cancer* 2013; 108: 1195-208.
26. SEER Training Modules. Summary staging. U.S. National Institutes of Health, National Cancer Institute. Available: <https://training.seer.cancer.gov/> [Accessed 16 March 2020].
27. Smith CL, Kricker A, Armstrong BK. Breast cancer mortality trends in Australia: 1921 to 1994. *Med J Aust* 1998; 168(1): 11-4.

**Table 1. Patient characteristics by TNM cancer stage; invasive breast cancers diagnosed in South Australia, 2000-2014***

| | I (n=6718) | II (n=5777) | III (n=1708) | IV (n=556) | Total (n=14759) | P |
|---|---|---|---|---|---|---|
| **Mean Age (year) (SD):** | 61.0 (12.2) | 60.0 (13.9) | 59.0 (14.3%) | 65.3 (15.2) | 60.6 (13.3) | <0.001 |
| **Age group:** | | | | | | <0.001 |
| <50 | 1143 (17.0%) | 1436 (24.9%) | 486 (28.5%) | 101 (18.2%) | 3166 (21.5%) | |
| 50-59 | 1877 (27.9%) | 1493 (25.8%) | 429 (25.1%) | 103 (18.5%) | 3902 (26.4%) | |
| 60-69 | 2121 (31.6%) | 1344 (23.3%) | 363 (21.3%) | 112 (20.1%) | 3940 (26.7%) | |
| 70-79 | 1072 (16.0%) | 929 (16.1%) | 267 (15.6%) | 124 (22.3%) | 2392 (16.2%) | |
| 80+ | 505 (7.5%) | 575 (10.0%) | 163 (9.5%) | 116 (20.9%) | 1359 (9.2%) | |
| **Country of birth:** | | | | | | 0.002 |
| Australia | 4101 (61.0%) | 3450 (59.7%) | 1035 (60.6%) | 332 (59.7%) | 8918 (60.4%) | |
| Other English-speaking countries | 985 (14.7%) | 858 (14.9%) | 226 (13.2%) | 75 (13.5%) | 2144 (14.5%) | |
| Non-English-speaking countries | 700 (10.4%) | 715 (12.4%) | 211 (12.4%) | 69 (12.4%) | 1695 (11.5%) | |
| Unknown | 932 (13.9%) | 745 (13.1%) | 236 (13.8%) | 80 (14.4%) | 2002 (13.6%) | |
| **SEIFA IRSD quintile:** | | | | | | <0.001 |
| 1 (most disadvantaged) | 1057 (15.7%) | 1063 (18.4%) | 319 (18.7%) | 131 (23.6%) | 2570 (17.4%) | |
| 2 | 1404 (20.9%) | 1126 (19.5%) | 332 (19.4%) | 125 (22.5%) | 2987 (20.2%) | |
| 3 | 1342 (20.0%) | 1165 (20.2%) | 355 (20.8%) | 112 (20.1%) | 2974 (20.2%) | |
| 4 | 1342 (20.0%) | 1168 (20.2%) | 341 (20.0%) | 88 (15.8%) | 2939 (19.9%) | |
| 5 (least disadvantaged) | 1572 (23.4%) | 1254 (21.7%) | 361 (21.1%) | 100 (18.0%) | 3287 (22.3%) | |
| **Remoteness:** | | | | | | 0.310 |
| Major city | 4978 (74.1%) | 4293 (74.3%) | 1290 (75.5%) | 418 (75.2%) | 10979 (74.4%) | |
| Inner regional | 760 (11.3%) | 651 (11.3%) | 186 (10.9%) | 57 (10.3%) | 1654 (11.2%) | |
| Outer regional | 783 (11.7%) | 653 (11.3%) | 193 (11.3%) | 64 (11.5%) | 1693 (11.5%) | |
| Remote | 162 (2.4%) | 141 (2.4%) | 32 (1.9%) | 13 (2.3%) | 348 (2.4%) | |
| Very remote | 34 (0.5%) | 39 (0.7%) | 7 (0.4%) | 4 (0.7%) | 84 (0.6%) | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Unknown | 1 (0.01%) | 0 | 0 | 0 | 1 (0.01%) | |
| **Diagnosis period:** | | | | | | 0.346 |
| 2000-2004 | 2022 (30.1%) | 1889 (32.7%) | 452 (26.5%) | 197 (35.4%) | 4560 (30.9%) | |
| 2005-2009 | 2368 (35.3%) | 1881 (32.6%) | 630 (36.9%) | 223 (40.1%) | 5102 (34.6%) | |
| 2010-2014 | 2328 (34.7%) | 2007 (34.7%) | 626 (36.7%) | 136 (24.5%) | 5097 (34.5%) | |
| **Vital status:** | | | | | | <0.001 |
| Died | 720 (10.7%) | 1186 (20.5%) | 582 (34.1%) | 436 (78.4%) | 2924 (19.8%) | |
| Alive | 5998 (89.3%) | 4591 (79.4%) | 1126 (65.9%) | 120 (21.6%) | 11835 (80.2%) | |
| **Cause of death:** | | | | | | <0.001 |
| Breast cancer | 209 (29.0%) | 680 (57.3%) | 460 (79.0%) | 391 (89.7%) | 1740 (59.5%) | |
| Other cancers | 170 (23.6%) | 136 (11.5%) | 42 (7.2%) | 19 (4.4%) | 367 (12.6%) | |
| Non-cancer | 341 (47.6%) | 370 (31.2%) | 80 (13.8%) | 26 (6.0%) | 817 (27.9%) | |

*P from one-way ANOVA for age in years and Chi-square or ranked tests for others (see Methods).
Vital status and cause of death from cancer registry, censoring on 31th Dec 2014.
SD: Standard deviation; SEIFA: Socioeconomic Index for Areas; IRSD: Index of Relative Socioeconomic Disadvantage.

**Table 2. Odds ratios (95% confidence intervals) for diagnosis with advanced (TNM III or IV) as opposed to more localized (TNM I or II) breast cancers diagnosed in 2000-2014 in South Australia* (N=14759)**

| Characteristic | Case numbers - advanced/all stages | Odds ratio for advanced stage (unadjusted) | Odds ratio for advanced stage** (adjusted) |
|---|---|---|---|
| **Age at diagnosis (years):** | | | |
| <50 | 587/3166 | 1.00 | 1.00 |
| 50-59 | 532/3902 | 0.69 (0.61-0.79) | 0.70 (0.62-0.80) |
| 60-69 | 475/3940 | 0.60 (0.53-0.69) | 0.60 (0.53-0.69) |
| 70-79 | 391/2392 | 0.86 (0.75-0.99) | 0.85 (0.74-0.98) |
| 80+ | 279/1359 | 1.13 (0.98-1.33) | 1.11 (0.95-1.31) |
| **Country of birth:** | | | |
| Australia | 1370/8918 | 1.00 | 1.00 |
| Other English-speaking countries | 301/2144 | 0.90 (0.79-1.03) | 0.91 (0.80-1.04) |
| Non-English-speaking countries | 280/1695 | 1.09 (0.95-1.26) | 1.08 (0.93-1.24) |
| Unknown | 316/2002 | 1.04 (0.91-1.18) | 1.02 (0.89-1.16) |
| **Diagnostic period:** | | | |
| 2000-2004 | 649/4560 | 1.00 | 1.00 |
| 2005-2009 | 853/5102 | 1.21 (1.08-1.35) | 1.20 (1.07-1.34) |
| 2010-2014 | 762/5097 | 1.06 (0.95-1.19) | 1.06 (0.95-1.19) |
| **Residential remoteness:** | | | |
| Major city | 1078/10979 | 1.00 | 1.0 |
| Inner regional | 243/1654 | 0.93 (0.81-1.08) | 0.96 (0.82-1.11) |
| Outer region/remote/very remote | 313/2126 | 0.94 (0.82-1.07) | 0.88 (0.77-1.02) |
| **SEIFA IRSD quintile:** | | | |
| 1 (most disadvantaged) | 450/2570 | 1.00 | 1.00 |
| 2 | 457/2987 | 0.85 (0.74-0.98) | 0.87 (0.75-1.00) |
| 3 | 467/2974 | 0.88 (0.76-1.01) | 0.88 (0.76-1.01) |
| 4 | 429/2939 | 0.81 (0.70-0.93) | 0.79 (0.68-0.92) |
| 5 (least disadvantaged) | 461/3287 | 0.77 (0.67-0.89) | 0.75 (0.65-0.87) |

*Adjusted odds ratios from logistic regression model including age, country of birth, diagnosis period, SES quintile, and residential remoteness.
SEIFA: Socioeconomic Index for Areas; IRSD: Index of Relative Socioeconomic Disadvantage.

**Table 3. Sub-hazard ratios (95% confidence intervals) for breast cancer-specific mortality in South Australia for invasive breast cancers diagnosed in 2000-2014 (N=14759)**

| Characteristic | Breast cancer death/death | Unadjusted SHR* | Adjusted SHR** |
|---|---|---|---|
| **TNM stage:** | | | |
| I | 209/720 | 1.00 | 1.00 |
| II | 680/1186 | 3.99 (3.42-4.65) | 3.87 (3.32-4.53) |
| II | 460/582 | 10.69 (9.09-12.57) | 10.87 (9.22-12.81) |
| IV | 391/436 | 45.82 (38.15-55.03) | 41.97 (34.78-50.65) |
| **Age at diagnosis (years):** | | | |
| <50 | 365/405 | 1.00 | 1.00 |
| 50-59 | 404/526 | 0.83 (0.77-1.02) | 1.10 (0.95-1.27) |
| 60-69 | 342/556 | 0.78 (0.68-0.90) | 1.05 (0.91-1.22) |
| 70-79 | 329/699 | 1.31 (1.13-1.52) | 1.43 (1.22-1.67) |
| 80+ | 300/738 | 2.22 (1.89-2.59) | 2.24 (1.90-2.66) |
| **Country of birth:** | | | |
| Australia | 1049/1777 | 1.00 | 1.00 |
| Other English-speaking countries | 247/412 | 0.98 (0.85-1.12) | 1.01 (0.87-1.17) |
| Non-English-speaking countries | 200/346 | 1.02 (0.87-1.18) | 0.98 (0.84-1.15) |
| Unknown | 244/389 | 1.08 (0.94-1.25) | 1.15 (1.00-1.33) |
| **Diagnostic period:** | | | |
| 2000-2004 | 884/1512 | 1.00 | 1.00 |
| 2005-2009 | 654/1076 | 0.81 (0.73-0.90) | 0.75 (0.67-0.83) |
| 2010-2014 | 202/336 | 0.62 (0.53-0.72) | 0.57 (0.48-0.67) |
| **Residential remoteness:** | | | |
| Major city | 1302/2186 | 1.00 | 1.00 |
| Inner regional | 185/313 | 0.99 (0.85-1.16) | 1.01 (0.86-1.20) |
| Outer regional/remote/very remote | 253/425 | 1.01 (0.88-1.15) | 0.97 (0.84-1.13) |
| **SEIFA IRSD quintile:** | | | |
| 1 (most disadvantaged) | 364/605 | 1.00 | 1.00 |
| 2 | 371/604 | 0.88 (0.76-1.02) | 0.93 (0.79-1.09) |
| 3 | 353/613 | 0.80 (0.69-0.93) | 0.85 (0.72-0.99) |
| 4 | 328/544 | 0.79 (0.68-0.92) | 0.85 (0.73-1.00) |
| 5 (least disadvantage) | 324/558 | 0.67 (0.58-0.78) | 0.73 (0.62-0.87) |

*Unadjusted SHRs derived from univariate competing risk regression modelling, deaths followed to December 31, 2014.

**Adjusted SHRs derived from multivariate competing risk regression model adjusting by including cancer stage, age, country of birth, diagnosis period, residential remoteness and SEIFA quintile.

SHR: Sub-hazard ratio; SEIFA: Socioeconomic Index for Areas; IRSD: Index of Relative Socioeconomic Disadvantage.

Figure 1. % of breast cancer survival by cancer stage in South Australia comparing with other countries during 2000-2014

Data source: see reference number 5 - Cancer Australia. National Cancer Control Indicators. Sydney: Cancer Australia, 2019. Available: https://ncci.canceraustralia.gov.au/ [Accessed 1 October 2019].

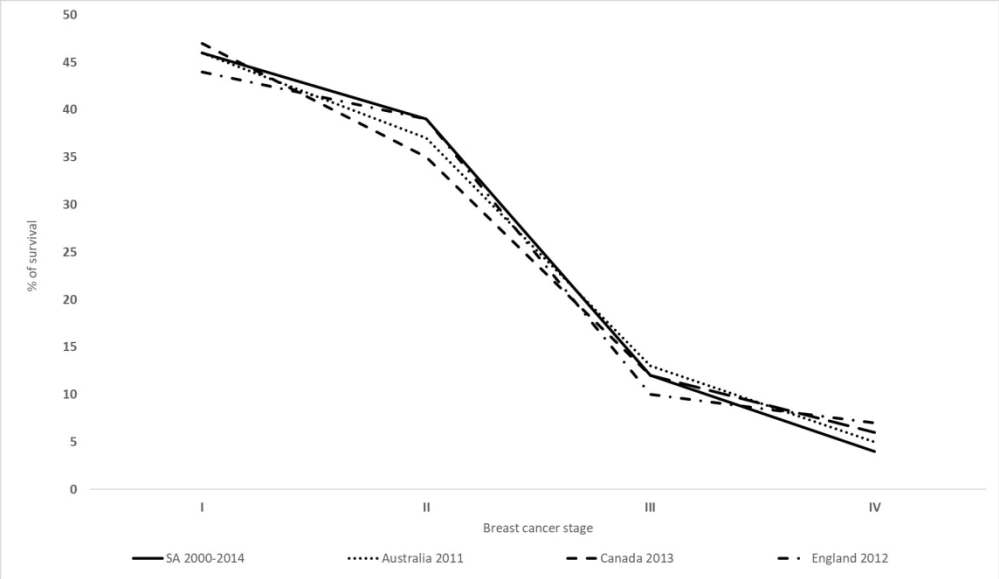


Figure 1. % of breast cancer survival by cancer stage in South Australia comparing with other countries during 2000-2014
Data source: see reference number 5 - Cancer Australia. National Cancer Control Indicators. Sydney: Cancer Australia, 2019. Available: https://ncci.canceraustralia.gov.au/ [Accessed 1 October 2019].

151x87mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

| | Item No | Recommendation | Page No |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 1 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 4 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 2 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 4,5 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 4,5 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 2,4,5 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 5,6 |
| 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 | 4,5 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 10 |
| Study size | 10 | Explain how the study size was arrived at | 4,5,6 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 5 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 6 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 6 |
| | | (*c*) Explain how missing data were addressed | 5,6 |
| | | (*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 | 14,16,17 |
| | | (b) Give reasons for non-participation at each stage | N/A |
| | | (c) Consider use of a flow diagram | N/A |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | 14-17 |
| | | (b) Indicate number of participants with missing data for each variable of interest | 14-17 |
| | | (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 | 14-17 |

| | | | |
|---|---|---|---|
| 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<br>(*b*) Report category boundaries when continuous variables were categorized<br>(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | 6-10 & 14-17<br>14-17<br>N/A |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 6-10 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 7-10 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 2, 10 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 7-10 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 7-10 |
| **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 | 11 |

*Give information separately for exposed and unexposed groups.

**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 http://www.strobe-statement.org.