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Geographical and spatial disparities in the incidence and survival of rare cancers in Australia

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Abstract

Rare cancers collectively account for around a quarter of cancer diagnoses and deaths. However, epidemiological studies are sparse. We describe spatial and geographical patterns in incidence and survival of rare cancers across Australia using a population-based cancer registry cohort of rare cancer cases diagnosed among Australians aged at least 15 years, 2007 to 2016. Rare cancers were defined using site- and histology-based categories from the European RARECARE study, as individual cancer types having crude annual incidence rates of less than 6/100 000. Incidence and survival patterns were modelled with generalised linear and Bayesian spatial Leroux models. Spatial heterogeneity was tested using the maximised excess events test. Rare cancers (n = 268 070) collectively comprised 22% of all invasive cancer diagnoses and accounted for 27% of all cancer-related deaths in Australia, 2007 to 2016 with an overall 5-year relative survival of around 53%. Males and those living in more remote or more disadvantaged areas had higher incidence but lower survival. There was substantial evidence for spatial variation in both incidence and survival for rare cancers between small geographical areas across Australia, with similar patterns so that those areas with higher incidence tended to have lower survival. Rare cancers are a substantial health burden in Australia. Our study has highlighted the need to better understand the higher burden of these cancers in rural and disadvantaged regions where the logistical challenges in their diagnosis, treatment and support are magnified.

KEYWORDS
Australia, geographical disparities, incidence, rare cancers, spatial modelling, survival

What's new?

Despite their high collective occurrence, research on the epidemiology and aetiology of individual rare cancer types is sparse. Here, the authors applied spatial mapping to a population-based cancer registry cohort of rare cancer cases diagnosed between 2007 and 2016. The findings reveal that

Abbreviations: ACT, Australian Capital Territory; ASGS, Australian Statistical Geography Standard; CI, confidence interval; CrI, credible interval; EHR, excess hazard ratio; HREC, Human Research Ethics Committee; ICD-O3, International Classification of Diseases for Oncology, third edition; IRR, incidence rate ratio; NOS, neoplasm not otherwise specified; NSW, New South Wales; NT, Northern Territory; QLD, Queensland; SA2, Statistical Area Level 2; SES, socioeconomic status; SIR, standardised incidence ratio.

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rare cancers collectively account for a substantial cancer burden in Australia, with marked geographical and spatial patterns for both incidence and survival. The study highlights the need to better understand the reasons behind the higher burden of rare cancers in rural and disadvantaged regions, where the logistical challenges for diagnosis, treatment, and support are magnified.

1 | INTRODUCTION

Rare cancers are a heterogenous group of diseases which, while individually uncommon,[1] collectively represent a substantial cancer burden[2-4]; comprising around a quarter of all cancers diagnosed in the United States,[2] Europe[3,5] and Australia.[6] Despite their high collective occurrence, research on the epidemiology and aetiology of individual rare cancer types can be challenging,[7] although risk factors commonly reported for rare cancers include smoking, alcohol, obesity, infectious agents, and occupational carcinogens.[8-10] In addition, clinical trials, effective treatment options and evidence-based guidelines for their management are limited.[7] As a consequence, medical and psychosocial outcomes for rare cancer types are worse than for more common cancer types, reflecting the unique challenges in their diagnosis, treatment, access to clinical expertise and supportive care needs.[2,5,7,11,12]

While spatial mapping has a long history of facilitating the understanding of disease aetiology and burden,[13] its application to rare cancer types has been minimal. International reports on geographical variations are limited to variations between countries[4,8,14] with the exception of one study on patterns by states/territories in Canada.[15] To date there has been no published investigation of how the burden of rare cancers varies by small geographical areas, nor variation by remoteness and residential area disadvantage. Given the geographical diversity of Australia and variation in population density nationwide, we address this gap in knowledge by using population-based cancer registry data to quantify broad geographical and spatial variations in incidence and survival for rare cancers across Australia. We could not report spatial patterns based on cancer mortality as an outcome, since information about usual residence at the time of death is not collected by many Australian cancer registries. These patterns were analysed for all rare cancers combined, which as a group presents unique challenges to patients and clinicians,[7] and has clear differences to other cancer types. This approach of combining individual rare cancer types is also consistent with a previous Canadian study.[15] We acknowledge that these patterns may vary for individual rare cancers, reflecting differences in aetiology. This information may help guide resource allocation, inform targeted strategies for the ongoing management of rare cancers and implementation of primary prevention programmes for known risk factors in high incidence areas.

2 | METHODS

2.1 | Study data

Data for all invasive cancers diagnosed in Australia between 2002 and 2016 was obtained from the population-based Australian Cancer Database.[16] Mortality status up to December 31, 2016 was determined through routine annual linkage of cancer records with the Australian National Death Index. While deaths may potentially be missed either due to missed links or people moving overseas, a recent study estimated that this possibility was small in Australia.[17]

The data set included details on the usual area of residence for each patient at time of cancer diagnosis, based on their Statistical Area Level 2 (SA2) as defined in the 2011 Australian Statistical Geography Standard (ASGS).[18] SA2s cover Australia without gap or overlap and are deemed to group together relatively homogenous subpopulations, while being socioeconomically relevant to their residents.

All analyses were restricted to persons aged at least 15 years at diagnosis and for survival analysis were further limited to those aged between 15 and 89 years. Cases without a known SA2 at diagnosis (n = 6839, 0.56%), and those with unknown age at diagnosis (n = 563, 0.05%) were excluded.

Regarding data quality indicators, around 1.2% (n = 14 634) of all cancer cases (n = 1 228 074) were detected by death certificates only, while 79 527 cases had "neoplasm not otherwise specified" (NOS) morphology codes. While the number of cases lost to follow-up in this cancer registry cohort is unknown, it is estimated to be low in Australian cancer registries.[17]

Estimated resident population data by age, sex and SA2 were obtained from the Australian Bureau of Statistics[19] and population mortality data by age, sex and SA2 for 2006 to 2016 were obtained from the Office of Births, Deaths and Marriages.[20]

2.2 | Rare cancers definition

All cancers were classified using a list of clinically relevant and histologically defined cancer types (RARECARE list),[8] developed by the European RARECARE consortium, chosen here to allow comparisons with international studies[8,14] and the only previous study on rare cancers epidemiology from Australia.[6]

The RARECARE list divides cancers according to their combined International Classification of Diseases for Oncology third edition, (ICD-O3) site (topography) and morphology codes into *two tiers*. The first (Tier-1) comprises major cancer entities in a clinical sense (eg, "soft tissue sarcoma") that direct patient referral policies while the second (Tier-2) categorises Tier-1 types into clinically distinct tumours (eg, "soft tissue sarcoma of limb").[1] In total there were 68 Tier-1 and 216 Tier-2 entities as of February 2019.[8] Since Tier-1 "EPITHELIAL TUMOURS OF THE SKIN" group[6] comprises basal and squamous cell skin carcinomas, which are not reported to Australian cancer

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registries, they were excluded from our study, leaving 67 Tier-1 and 214 Tier-2 entities for our study.

Cancers were defined as "rare," or "common" based on their Tier-2 annual crude incidence rates (incidence of <6and ≥6 cases per 100 000 people respectively).[8] Apart from sex-specific sites, rates were based on the total population (ie, males and females combined).

All Tier-2 cancers (from RARECARE list) which met the rarity threshold (annual crude incidence rate <6 cases per 100 000 people) were collectively categorised as rare cancers. Detailed analyses as described below with code in Supplementary Methods restricted to those cancers.

2.3 | Statistical analysis

Generalised linear models were fitted with Stata/MP version 16 (StataCorp, TX). Bayesian spatial models were implemented in R version 4.0.3.[21] Incidence models were fitted with the CARBayes package (version 5.2.5)[22] while survival models were fitted with WinBUGS1.4.3[23] through the R2WinBUGS package (version 2.1-21).[24] All other analyses were performed with Stata/MP version 16 (StataCorp, TX).

2.3.1 | National estimates

Crude and age-standardised incidence rates (to the 2001 Australian standard population) across all SA2's in Australia for all Tier-1 and Tier-2 cancers were calculated over the study period (2007-2016). Estimated resident population data for overall Australia by age, sex, and year[25] were used as the person-time for these calculations. For sex-specific cancers, incidence rates were estimated using the relevant sex-specific population.

Directly age standardised incidence rates for all rare cancers combined were calculated using the Australian 2001 standard age distribution. For incidence analysis, 10 years of data were aggregated, spanning 2007 to 2016. Relative survival was calculated using the period approach.[26] The "at risk" period for survival analyses was 2007 to 2016, hence individuals were included in the population at risk (prevalent) for each year between 2007 and 2016 that they survived after having been diagnosed no more than 5 years previously (earliest diagnosis year was 2002). For people with multiple rare cancers, all cases were counted in the incidence analysis while for survival analysis only the first case was considered which was at risk during the study period.

Survival was measured in days from the date of diagnosis to one of: death or the study endpoint (December 31, 2016), whichever came first. Cases alive at the end of follow-up were censored.

Area-level socioeconomic status (SES) was measured by the 2011 census-based Index for Relative Socioeconomic Advantage and Disadvantage.[27] Remoteness was defined using the 2011 Remoteness Areas[28] classification with remote and very remote categories combined.

2.3.2 | Generalised linear models

Broad geographical patterns in both incidence and survival for rare cancers were explored using multivariable Poisson generalised linear models[29] with age group, sex, area-level SES, remoteness and state/territory as covariates. For the incidence model, the offset was the log of the population at risk. Relative survival models[30] were used to capture cancer deaths up to 5 years since diagnosis and were further adjusted for follow-up time (risk period) and broad cancer type.

A stepwise model building process was used, starting with the fully adjusted model. Variables were kept in models based on likelihood ratio tests ($P < .20$). While interaction terms between different covariate pairs were also tested because of known correlations between these area-level variables, they were omitted in favour of a more parsimonious model as their inclusion did not improve model fit ($P \geq .20$) or alter the magnitude and confidence intervals of coefficients in the final main-effects models.

Poisson relative survival models[30] (Supplementary Methods) were used to calculate the excess hazard of death for the cohort compared to the age- and sex-matched population mortality. Expected survival was calculated using the Ederer II estimator.[30] Second-order interaction terms between each covariate and risk period were also tested but not included in the final model as the effects were weak ($.10 < P < .20$) and their inclusion did not improve the model fit substantially or alter the model coefficients.

Exponentiated coefficients from the incidence and survival models[30] are presented as incidence rate ratios (IRRs) or excess hazard ratios (EHRs) respectively, along with 95% confidence intervals (CIs). The statistical significance of individual coefficients and interaction terms were assessed with the Wald test (significant if $P < .05$, two-sided). Marginal incidence rates or survival, stratified by area-level factors, were also estimated by sex and sex-adjusted for all persons.[31]

2.3.3 | Bayesian spatial models

Bayesian spatial incidence and relative survival models (with age, sex, and broad cancer type as covariates) and with the Leroux prior for the spatial component[32] were fitted for males, females, and persons at the SA2 level as used in the Australian Cancer Atlas.[33] The models used a Poisson distribution for the observed counts of cases or deaths within 5 years with the log of the corresponding expected counts as an offset variable and included a spatial term incorporating adjacent neighbours. The Leroux conditional autoregressive prior, which incorporates both spatial and random area-level variation, was placed on the spatial term for each area. This prior avoids the identifiability difficulties of the Besag-Yorke-Mollié model[34] which has two separate terms for each area; one each for spatial and random variation.[34] These models estimated standardised incidence ratios (SIRs, incidence) or EHRs (survival) for each SA2, smoothed over neighbouring areas, to provide information on spatial patterns while protecting confidentiality and distinguishing real spatial patterns from random

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variation. For each area, the models generated a probability distribution of potential values for each of the unknown parameters including the SIR and EHR, and these distributions were used to generate credible intervals (CrIs) that represented the range of probable values for these parameters (Supplementary Methods). Example of R code are available in Supplementary Methods.

The median values of the SA2-specific modelled estimates were mapped using a diverging colour gradient, where pale yellow (cream) indicates the Australian average (= 1), orange/red shades higher than average and blue lower than average incidence or excess deaths. The colour gradient was linear on the log scale. The same colour scheme was used for graphs showing the ranked smoothed estimate with the associated 90% CrIs from the spatial models.

For additional context, summary box plots showing the distribution of the smoothed SA2-specific estimates by broad geographical categories were also included.

Evidence for spatial variation between small areas was assessed using Tango's Maximised Excess Events Test which compares the modelled numbers of diagnoses and deaths with the corresponding expected counts.[35]

TABLE 1 Number of diagnosed cases (percentage) and Incidence rate ratios (IRRs) [95% CI] from multivariable generalised linear model, rare cancers, Australia 2007 to 2016

Variable	N (col %)	Incidence rate ratios [95% Confidence intervals][a,b]
Sex		*P* < .001
Male	155 972 (58.3)	1.56 [1.55, 1.57]
Female	111 646 (41.7)	1.00
Age groups (yr)		*P* < .001
15-19	2775 (1.0)	0.14 [0.14, 0.15]
20-24	3758 (1.4)	0.18 [0.17, 0.18]
25-29	5306 (2.0)	0.24 [0.24, 0.25]
30-34	6427 (2.4)	0.31 [0.30, 0.32]
35-39	7919 (3.0)	0.38 [0.37, 0.39]
40-44	9984 (3.7)	0.48 [0.47, 0.49]
45-49	13 973 (5.2)	0.69 [0.68, 0.71]
50-54	19 504 (7.3)	1.00
55-59	24 816 (9.3)	1.40 [1.37, 142]
60-64	30 019 (11.2)	1.89 [1.86, 1.93]
65-69	32 914 (12.3)	2.52 [2.48, 2.56]
70-74	31 704 (11.8)	3.22 [3.16, 3.28]
75-79	30 051 (11.2)	3.98 [3.91, 4.05]
80-84	25 522 (9.5)	4.55 [4.46, 4.63]
85+	22 946 (8.6)	3.15 [3.08, 3.21]
Remoteness[c]		*P* < .001
Major cities	180 265 (67.4)	1.00
Inner regional	55 935 (20.9)	0.97 [0.96, 0.98]
Outer regional	26 588 (9.9)	0.98 [0.96, 0.99]
Remote	4830 (1.8)	1.01 [0.98, 1.04]
Area-level disadvantage[d]		*P* < .001
Most advantaged	49 335 (18.4)	1.00
Q4	49 339 (18.4)	1.05 [1.03, 1.06]
Q3	54 960 (20.5)	1.09 [1.08, 1.11]
Q2	55 823 (20.9)	1.14 [1.12, 1.15]
Most disadvantaged	58 161 (21.8)	1.21 [1.19, 1.22]
State/territory		*P* < .001
New South Wales	91 221 (34.1)	1.00
Victoria	64 045 (23.8)	0.93 [0.92, 0.94]
Queensland	53 785 (20.1)	1.01 [1.00, 1.02]
South Australia	21 138 (7.9)	0.94 [0.93, 0.95]
Western Australia	25 582 (9.6)	0.96 [0.95, 0.97]
Tasmania	6667 (2.5)	0.95 [0.92, 0.97]
Northern Territory	1833 (0.7)	0.97 [0.93, 1.02]
Australian Capital Territory	3347 (1.3)	0.92 [0.88, 0.95]

[a]Estimated using multivariable generalised linear Poisson models adjusted for all variables in table.
[b]Wald's joint test of coefficients for multivariable generalised linear Poisson models.
[c]Remote areas were defined by the Remoteness Areas 2011 classification with remote and very remote areas combined.
[d]Area-level disadvantage was defined by the 2011 SEIFA Index of Relative Socioeconomic Advantage and Disadvantage.

3 | RESULTS

Of all invasive cancer cases that could be assigned a Tier-1 rare cancer entity (n = 1 193 743) including both rare and common cancers, based on their ICD-O3 topography and morphology codes, around 6% (n = 79 527) had a NOS morphology code and hence could not be assigned a Tier-2 entity (Table S1). These records were excluded from the study cohort.

Rare cancers (defined by Tier-2; n = 268 070) collectively comprised 21.8% of all invasive cancer cases (n = 1 228 074) diagnosed in Australia between 2007 and 2016 (Figure S1). They also accounted for 26.6% of all cancer deaths among persons considered to be "at risk" between 2007 and 2016.

3.1 | Incidence

The overall age standardised incidence rates of rare cancers in Australia were 109.5 per 100 000 persons (95% CI 109.1-109.3). Rates were higher among males (134.7 per 100 000 [134.3-135.6]) than females (87.3 [86.7-87.7]).

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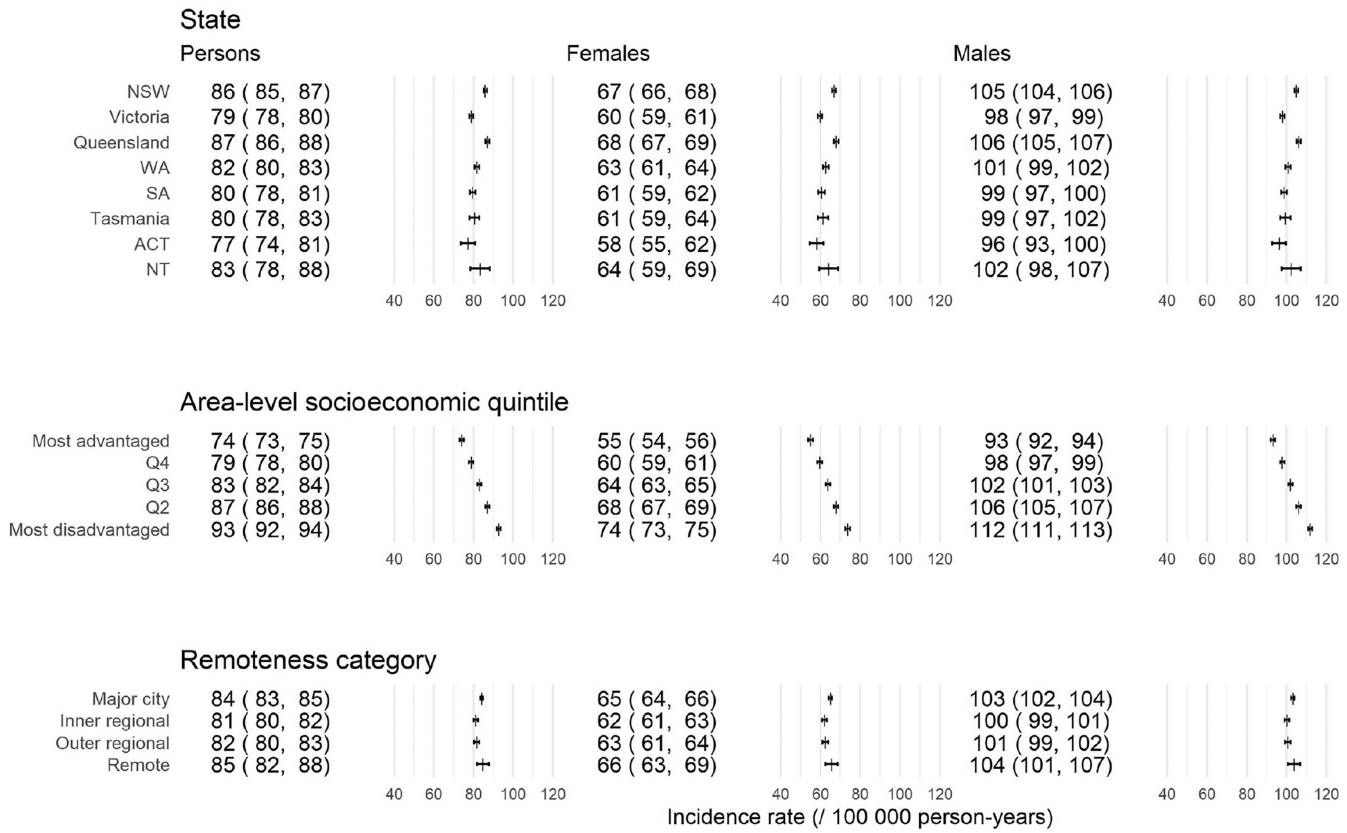

FIGURE 1 Age-adjusted rare cancer incidence rates (per 100 000 person-years) by sex and state/territory, area-level socioeconomic quintile and remoteness category, with 95% confidence intervals. ACT, Australian Capital Territory; NSW, New South Wales; NT, Northern Territory; SA, South Australia; WA, Western Australia

3.1.1 | Demographic and geographical variation

After full adjustment, males were 1.6 times more likely to be diagnosed with rare cancers than females (IRR 1.56 [95% CI 1.55-1.57]) (Table 1). Incidence rates increased with age and area-level disadvantage (IRR most disadvantaged: most advantaged 1.21; 1.19-1.22) and were lower in rural areas than major cities (Table 1; Figure 1). Residential state/territory was strongly associated with incidence ($P < .001$) with the highest marginal adjusted incidence rates (around 86 cases per 100 000 person years) in New South Wales (NSW) and Queensland (QLD) and the lowest (77 cases per 100 000 person years) in the Australian Capital Territory (ACT) (Figure 1). Geographical patterns by sex were similar to those for persons, with this being assessed by looking at the interaction terms between sex and the geographical covariates (remoteness, SES, state/territory) which were not statistically significant (all $P \geq .20$).

3.1.2 | Spatial variation

There was strong evidence of spatial variation in rare cancer incidence across Australia during the study period among males, females, and persons (all maximised excess events test: $P < .001$). Maps of the smoothed SA2-specific median SIR estimates (Figure 2) for persons from the spatial incidence model showed higher than average diagnosis rates (orange/red shades) in the Northern Territory (NT), far north QLD and rural NSW. In terms of capital cities, for Melbourne, the majority of areas had lower incidence than average whereas for all areas in Canberra, the incidence was either similar to (cream shades) or lower than the national average (blue shades). However (as expected) patterns for other capital cities were mixed with no predominant pattern. Patterns by sex (Figure S2) were similar to those for persons.

We used the 90% CrIs to assess the evidence that an area's incidence is different to the Australian average. If the 90% CrI for a specific small area was either entirely above or entirely below one, this provided evidence of a "real difference" between the incidence for that area and the national average. Based on this criterion, the models indicated that 19% (for persons), 21% (males) and 10% (females) of SA2s had below average incidence, and 14%, 16% and 7% of areas had above average incidence of rare cancers for persons, males, and females, respectively.

While there was little evidence that the distribution of the median SIR varied substantially across remoteness or SES categories (Figure S3A,B) areas considered remote or most disadvantaged tended to have higher SIRs compared to those from major cities or most advantaged areas, respectively. SIRs were distributed fairly evenly around one for all states/territories with the exception of ACT where the SIRs were lower (Figure S3C). Plots of the ranked median SIRs

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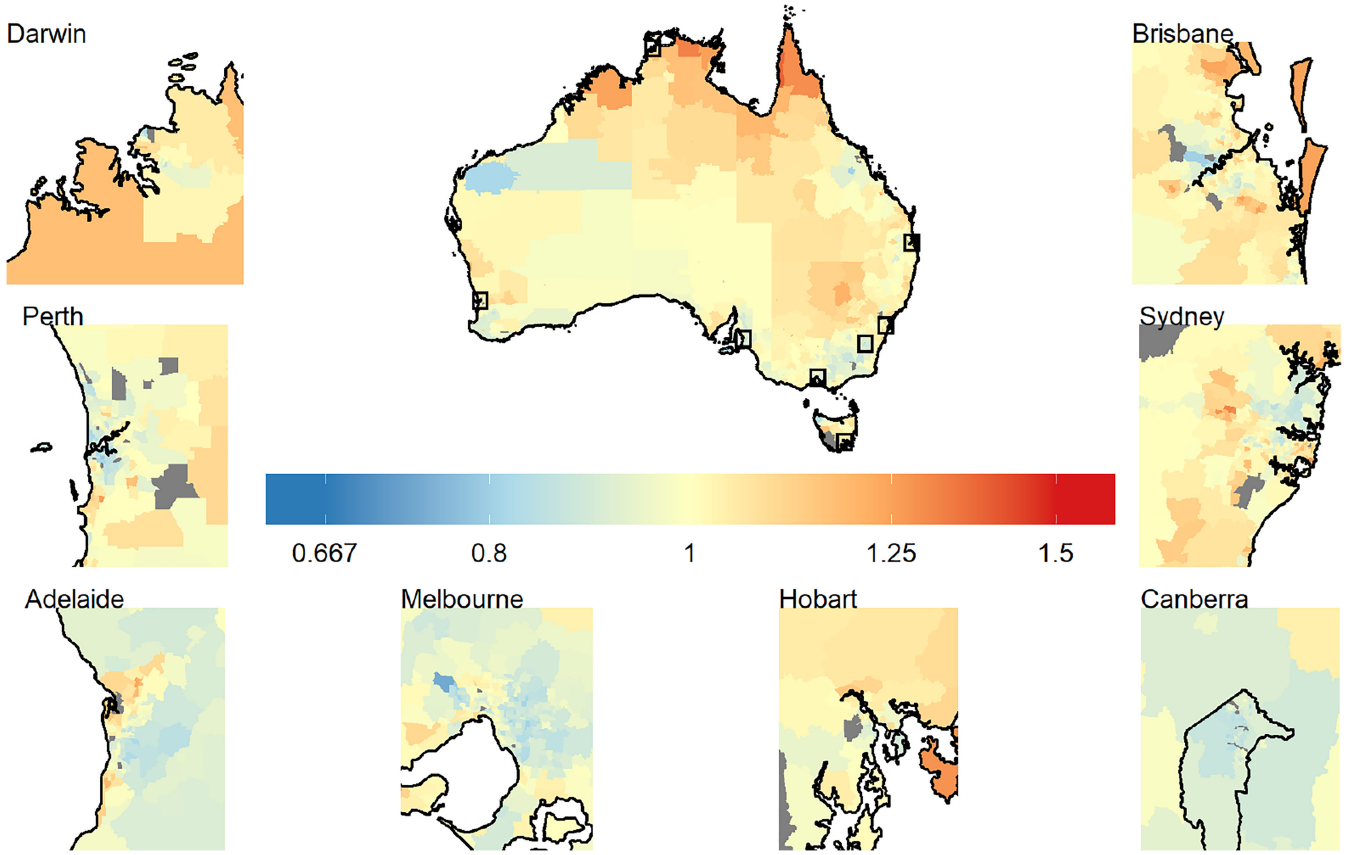

FIGURE 2 Maps of the smoothed standardised incidence ratios (SIRs) for rare cancers for persons by Statistical Area Level 2, 2007 to 2016, with insets of the state and territory capitals. The map for Canberra includes the boundary between the Australian Capital Territory and New South Wales. An SIR with value 1 indicates that incidence is the same as the national average

with their associated 90% CrIs grouped by broad geographical variables (Figures S4-S6) indicated that smoothed rates often had nonoverlapping CrIs suggesting that the differences between lowest and highest ranked geographical areas were real.

3.2 | Survival

Five-year relative survival among rare cancer cases that were prevalent during 2007 to 2016 was 53.2% (95% CI 52.8%-53.3%) which was lower than for common cancers (79.3% 95% CI 79.2%-79.4%).

Annually there were on average 12 289 deaths within 5 years of a rare cancer diagnosis among persons during the study period, of which 11 019 (males 6763; females 4256) were more than would be expected (ie, excess deaths) based on the age-and sex-matched population mortality.

3.2.1 | Geographical

All covariates in the fully adjusted model were significantly associated ($P < .001$) with 5-year relative survival (Table 2). Males, older persons (75-89 years) and residents of remote areas had lower survival (higher excess hazard of death). Survival also decreased with increasing residential disadvantage with the most disadvantaged areas having a 35% (EHR 1.35, 95% CI: 1.32-1.38) higher risk of death (vs least disadvantaged) within 5 years of diagnosis. By state/territory, the EHR was highest in NT and lowest in Victoria and QLD (vs NSW) with an adjusted survival of 36% (35%-38%) in NT and around 53% in Victoria and QLD (Figure 3). The marked SES gradient was also evident with an adjusted 5-year survival of 56% in most advantaged and 46% in most disadvantaged areas, respectively. Geographical patterns by sex mirrored those for persons (no significant interaction effects with sex; $P \geq .20$).

3.2.2 | Spatial variation

There was strong evidence of spatial variation in 5-year relative survival for rare cancers for both sexes and persons (all maximised excess events test: $P < .001$). Maps of the smoothed EHRs (adjusted for age, sex, broad cancer type, based on survival probability) (Supplementary Methods) for persons from the spatial survival model (Figure 4) indicated that the majority of areas in northern, western and central Australia along with Tasmania had lower survival (higher EHR) than the national average (orange/

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TABLE 2 Number of deaths and excess hazard ratios (EHRs) [95% CI] from multivariable generalised linear model for 5-year relative survival, rare cancers, Australia, 2007 to 2016

Variable	N deaths (col %)[a]	Excess hazard ratios [95% Confidence intervals][b,c]
Sex		*P* < .001
Male	87 200 (61.2)	1.20 [1.18, 1.21]
Female	55 283 (38.8)	1.00
Age groups (yr)		*P* < .001
15-54	19 228 (13.5)	0.43 [0.42, 0.44]
55-64	27 369 (19.2)	1.00
65-74	39 803 (27.9)	1.38 [1.35, 1.41]
75-89	56 083 (39.4)	2.09 [2.04, 2.14]
Remoteness[d]		*P* < .001
Major cities	94 180 (66.1)	1.00
Inner regional	30 693 (21.5)	0.97 [0.95, 0.98]
Outer regional	14 804 (10.4)	0.98 [0.96, 1.01]
Remote	2806 (2.0)	1.15 [1.10, 1.21]
Area-level disadvantage[e]		*P* < .001
Most advantaged	23 684 (16.6)	1.00
Q4	24 792 (17.4)	1.12 [1.09, 1.14]
Q3	28 932 (20.3)	1.19 [1.16, 1.21]
Q2	31 034 (21.8)	1.26 [1.24, 1.29]
Most disadvantaged	34 041 (23.9)	1.35 [1.32, 1.38]
State/territory		*P* < .001
New South Wales	49 989 (35.1)	1.00
Victoria	32 740 (23.0)	0.92 [0.90, 0.93]
Queensland	27 459 (19.3)	0.89 [0.88, 0.91]
South Australia	12 243 (8.6)	1.01 [0.99, 1.04]
Western Australia	13 516 (9.5)	1.01 [0.99, 1.04]
Tasmania	3755 (2.6)	1.02 [0.98, 1.06]
Northern Territory	1158 (0.8)	1.45 [1.35, 1.55]
Australian Capital Territory	1623 (1.1)	1.08 [1.02, 1.15]

[a]Number of deaths within 5-years of diagnosis among patients who were diagnosed with a rare cancer from 2002 to 2016 and who were "at risk" at some point between 2007 and 2016 (inclusive).
[b]Estimated using multivariable generalised linear Poisson relative survival models adjusted for all variables in table. Models also adjusted for broad cancer type and years since diagnosis (risk period).
[c]Wald's joint test of coefficients for multivariable generalised linear Poisson models.
[d]Remote areas were defined by the Remoteness Areas 2011 classification with remote and very remote areas combined.
[e]Area-level disadvantage was defined by the 2011 SEIFA Index of Relative Socioeconomic Advantage and Disadvantage.

red shades). In contrast, areas in Victoria and along the coastal region of eastern and southern mainland Australia (cream-coloured) had similar survival to the national average. While most areas in Melbourne and Brisbane had higher survival (blue shade), all areas in Darwin had lower survival than the average. There was no evidence that these patterns varied markedly by sex (Figure S7).

As with incidence, if the 90% CrIs for the mapped EHRs were either completely above or completely below one, this provided evidence for a real survival difference in that area compared to the national average. The models indicated that 16%, 21% and 13% of SA2s had lower survival and 14%, 17% and 10% of areas had higher survival than average for persons, males, and females, respectively. Plots of the ranked median EHRs with their associated 90% CrIs grouped by remoteness, SES, or state/territory (Figures S8-S10) give an indication of the uncertainty of the mapped estimates.

There was a clear gradient in the distribution of the median EHR across remoteness categories with median values being lower than one for major cities compared to remote areas where almost all median EHRs were higher than one (Figure S3D). A similar pattern was seen by SES with the median values being lower than one for most advantaged areas and higher than one for most disadvantaged areas (Figure S3E). There was evidence that the distribution of the median EHR varied by state/territory with lower survival for NT and higher survival for ACT (Figure S3F).

4 | DISCUSSION

In this population-based study we found that rare cancer types collectively comprised around a fifth of all cancer diagnoses and a quarter of cancer-related deaths between 2007 and 2016 nationally highlighting their substantial contribution to the overall cancer burden in Australia. There was also substantial evidence for geographical and spatial variation in both incidence and survival across the country. In particular, more disadvantaged, and rural/remote areas had higher incidence and poorer survival.

While the definition of rare cancers varies, our estimate of around 22% of all cancers being rare cancer types is consistent with other Australian (17%-22%)[6,36] and international (15%-24%) studies.[2,3,5,14,15,37] Although international comparisons regarding survival should be made cautiously, given that there are likely to be differences in the case mix of individual cancer types categorised as rare cancers, our 5-year relative survival estimates (51%-56%) were in the same range as estimates for the United States,[2,8] Central and Northern Europe[4,5] and better than the combined estimate for Europe of around 48%.[1,3] Survival estimates for common cancers were also consistent with previously reported estimates for Western Australia[6] and the United States[2] while higher than European values.[1,5]

We found a strong association between increasing incidence of rare cancers in more socioeconomically disadvantaged areas. That a similar association held with survival outcomes, with more disadvantaged areas having poor survival, served to magnify the greater burden that people living in disadvantaged areas faced in relation to these rare cancer types. That these patterns remained even after adjusting for state/territory and residential remoteness, is a measure of the strength of this effect. To the best of our knowledge, such differentials for rare cancer incidence and survival have not been

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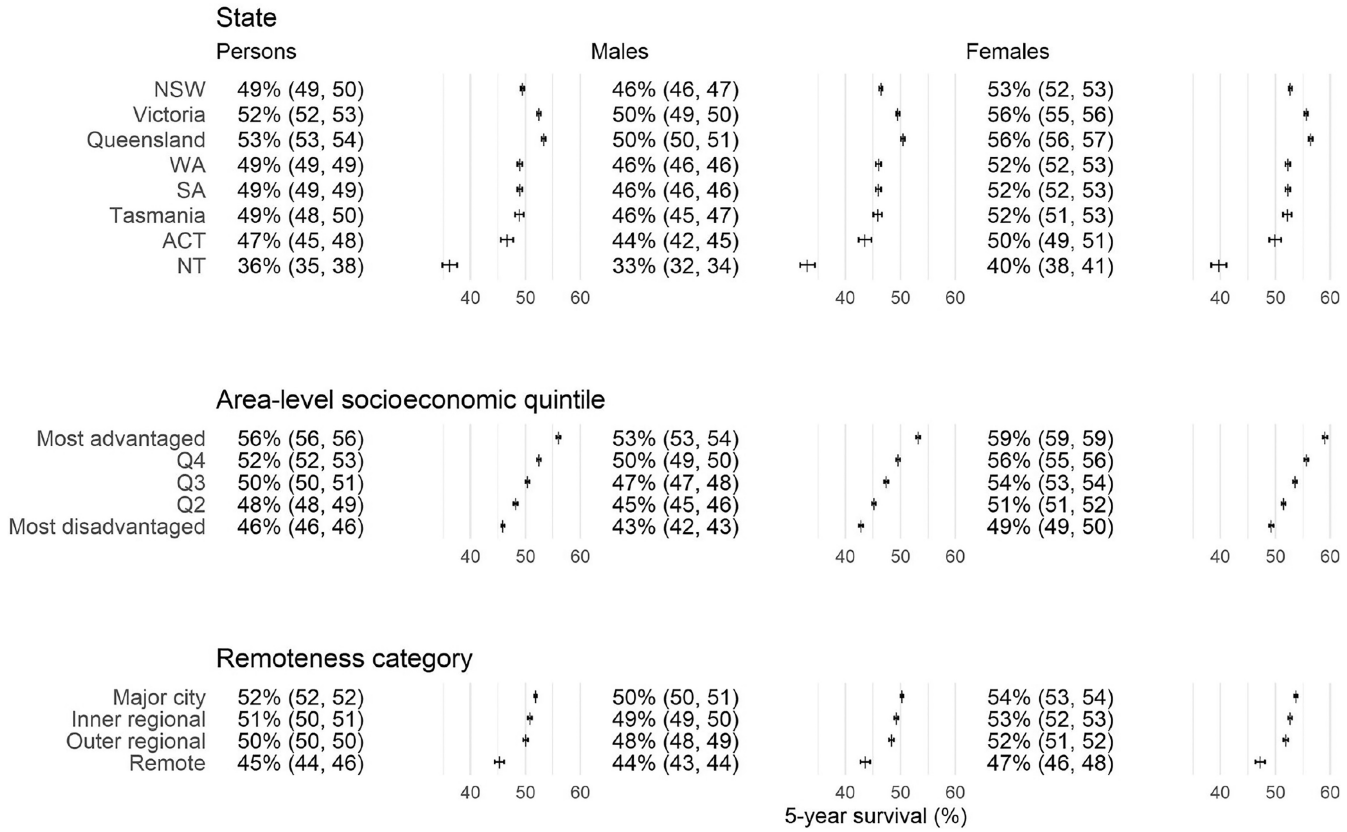

FIGURE 3 Age-adjusted, 5-year relative survival and 95% confidence intervals for rare cancers by sex and state/territory, area-level socioeconomic quintile and remoteness category, with 95% confidence intervals. ACT, Australian Capital Territory; NSW, New South Wales; NT, Northern Territory; SA, South Australia; WA, Western Australia

reported previously. The observed geographical variation in incidence suggests that there may be potentially modifiable risk factors for rare cancer types that require further research, while the survival disparities may be consistent with their greater financial, environmental, and logistical barriers,[38] as well as higher prevalence of chronic diseases[39] and poorer access to health care.[40]

Australia is spatially diverse, with the population being heavily concentrated in urban areas of south eastern coastal regions.[41] A lack of cancer services outside major cities[42] means that rural cancer patients in general often face long travel times to access specialised medical care, a potential driver potential for remoteness disparities in cancer outcomes.[43] These problems are likely to be magnified for rare cancers given that specialised rare cancer centres are concentrated along major cities in the populous south-east coastal area of Australia.[44] International studies have shown that reduced access to health care practitioners with experience in rare cancers may lead to diagnostic delays and impact survival.[5,7] There is international evidence that prognostic outcomes for rare cancers improve when their diagnosis and care occur at high volume specialised centres[5,45] thereby ensuring multidisciplinary expertise and potential access to collaborative networks and clinical trials.

Known risk factors for rare cancers include tobacco for most epithelial (ie, involving organs) rare cancers and leukaemias; alcohol for epithelial cancers of head and neck, liver and oesophagus and obesity for many epithelial cancers.[8] Infectious agents are associated with several epithelial cancers, lymphomas, and Kaposi sarcomas.[46] Occupational exposures have also been linked to many rare cancers including asbestos for mesothelioma and vinyl chloride for liver angiosarcoma.[9,10] However, quantifying the impact that these and other exposures had on geographical patterns in cancer incidence would be challenging.

Hence, another possible reason for the spatial differences is differences in the distribution of risk factors across population subgroups. For example, remote and disadvantaged Australians are known to have higher prevalence of lifestyle-related health risk behaviours.[39] Given the lack of data on small area variations in the prevalence of risk factors as well as the lag time between exposure and cancer diagnosis our ability to draw any definitive associations with exposure patterns was limited. In addition, we have no information about the residential history of cancer patients prior to their cancer diagnosis. However, a recent study on spatial patterns of mesothelioma in Australia suggested that some of the geographical patterns in diagnosis were consistent with the location of mines and asbestos-related industries in the past.[47] Our ability to quantify the associations with other potentially relevant factors was also limited by the small number of cases and a lack of data on individual

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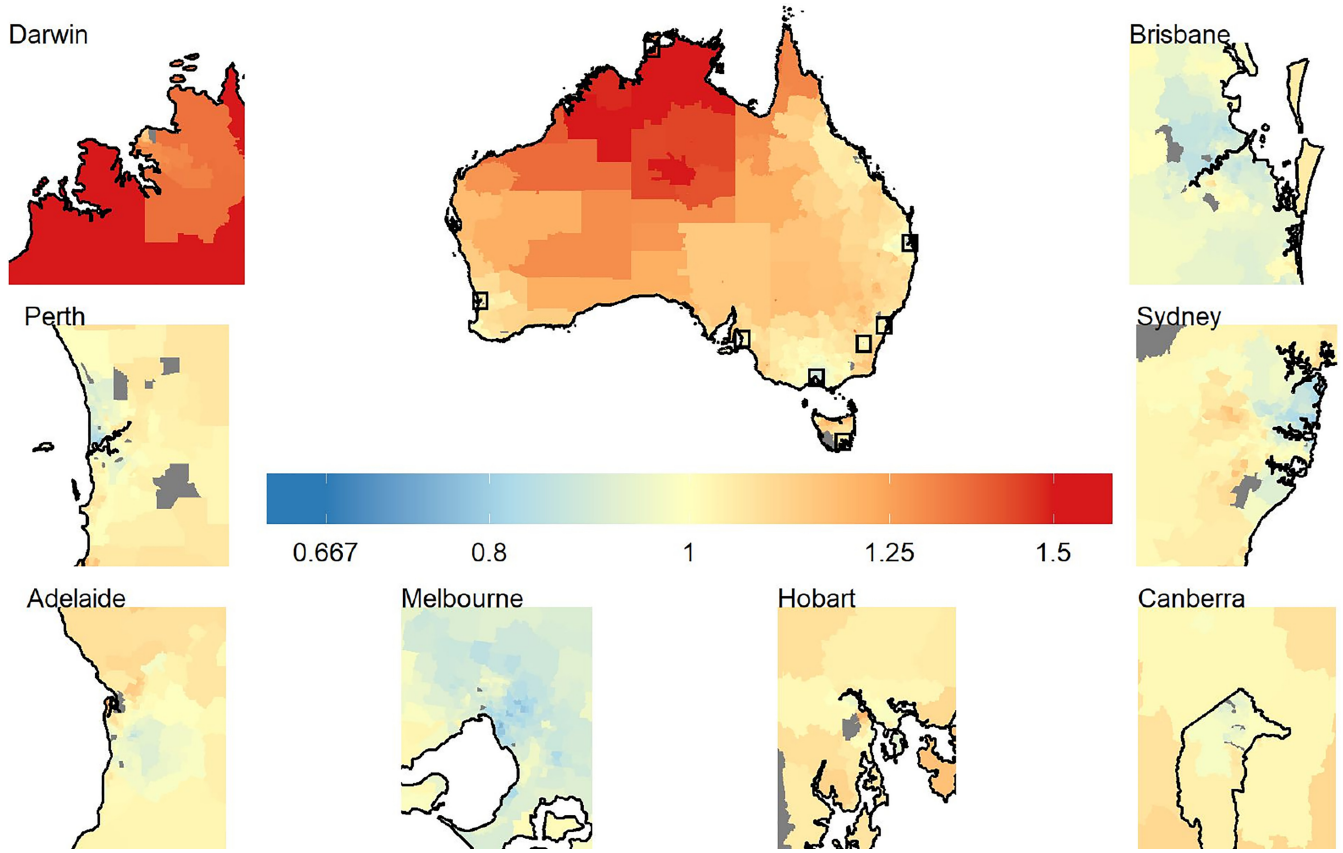

FIGURE 4 Maps of the excess hazard ratios (EHRs) for persons within 5 years of a rare cancer diagnosis by Statistical Area Level 2, 2007 to 2016, with insets of the state and territory capitals. The map for Canberra includes the boundary between the Australian Capital Territory and New South Wales. An EHR with value 1 indicates that survival is the same as the national average

characteristics and potential risk factors. Such data are not routinely collected by Australian population-based cancer registries.

Geographical and spatial differences in rare cancer incidence across Australia may also reflect variations in the proportion of microscopically verified cases and/or those that could not be assigned specific histology codes due to subtle differences in diagnostic capabilities or pathology reporting.

4.1 | Strengths and limitations

Study strengths include the use of high-quality comprehensive population-based cancer registry data[16] with national coverage and the use of Bayesian spatial hierarchical models to generate robust small-area incidence or survival estimates while preserving data confidentiality. Spatial analyses were complemented by describing broader geographical patterns across area-level remoteness and SES.

A reliable epidemiological description of rare cancers requires a low proportion of cases detected by death certificates only and those with NOS morphology. Both these data quality indicators for our study were at the lower end of international standards[1,6,8] While we cannot test the possibility that excluded cases may have impacted geographical differences, given their low numbers this is considered unlikely.

We used combinations of topology and morphology codes as defined by the RARECANCER project[8] to classify all cancer cases in our cohort. These combinations reflected European cancer registry coding practices at the time of their publication, and so have not been adjusted to reflect Australian-specific coding practices nor the recently added ICD-O3.2 codes.[48] In our study, around 3% of all cancer cases from Australian cancer registries could not be assigned a Tier-1 cancer entity, in addition to around 6% that could be assigned a Tier-1 but not Tier-2 cancer entity. However, several studies have validated the use of the RARECANCER list in describing rare cancer epidemiology in non-European settings,[2,6,14,15] and its use enables international comparisons.[8,14]

Overall, around 7% of all cases in the initial cohort had NOS morphology codes, meaning they could not be assigned to a specific (rare) cancer Tier-2 entity. Therefore, although these cases contributed to overall incidence estimates, the true incidence of rare cancers may have been underestimated and so could be higher than 22%.

5 | CONCLUSIONS

While each type of rare cancer affects only a small number of people, collectively they represent a substantial public health burden in

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Australia. Our study has highlighted the considerable small area geographical variation in the overall incidence and survival of rare cancers across Australia. It is crucial we better understand the reasons for the higher incidence and lower survival among residents of rural and disadvantaged regions where the logistical barriers to diagnosis and treatment of these cancers are likely to be magnified. Results presented here may be useful as benchmarks for future studies and to form a framework for further research into key factors associated with the geographical and spatial patterns identified here; these in turn could inform the development of strategies to achieve improved outcomes.

AUTHOR CONTRIBUTIONS

The authors Peter D. Baade, Joanne F. Aitken, Jessica K. Cameron and Paramita Dasgupta devised the project and the main conceptual ideas, Peter D. Baade coordinated and administered the study; Paramita Dasgupta, Jessica K. Cameron, Richard W. Trevithick and Susanna M. Cramb developed the methodology and statistical coding; Paramita Dasgupta carried out the statistical analysis and visualisation; Paramita Dasgupta drafted the manuscript, Peter D. Baade contributed to the original draft of the manuscript and all authors; Peter D. Baade, Paramita Dasgupta, Jessica K. Cameron, Joanne F. Aitken, Richard W. Trevithick, Susanna M. Cramb and Kerrie Mengersen refined and approved the submitted version. All authors provided critical feedback. Each author has participated sufficiently in the work and takes responsibility for appropriate portions of the content. The work reported in the article has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interests.

DATA AVAILABILITY STATEMENT

The unit record data that support the findings of our study were obtained from the Australian Cancer Database which is held by the Australian Institute of Health and Welfare. The data may be requested from the Australian Institute of Health and Welfare (subject to ethical approval). Please look at website (https://www.aihw.gov.au/our-services/data-on-request) to find information on how to request data from the Australian Institute of Health and Welfare. Restrictions apply to the availability of these data, which were used under licence for our study. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

Ethics approval was obtained from the Human research ethics committees (HRECs) of Griffith University (EC00162, Reference: 2018/280), the Northern Territory Department of Health and Menzies School of Health Research (EC00153, Reference: 2016-2720), Australian Capital Territory Health. (EC00100, Reference: ETHLR.16.235), NSW Population & Health Services (EC00410, Reference: 2019/ETH01656) and Queensland University of Technology (EC00171; Reference: 1600000880). The data custodians for each of the eight Australian state and territory cancer registries, to which notification of all invasive cancers (except keratinocyte skin cancers) is a statutory requirement, provided approval for data access.

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SUPPORTING INFORMATION

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