A population-based study of progression to metastatic prostate cancer in Australia

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A B S T R A C T

Background: We used population-based data from the New South Wales Central Cancer Registry (CCR) to describe the patterns of progression to metastatic disease in Australian men diagnosed with non-metastatic prostate cancer.

Methods: Data for all non-metastatic prostate cancer cases diagnosed 1993–2002 and followed to the end of 2007 were analysed. The outcome was progression to metastatic disease, identified by metastatic episode notifications in the CCR or by prostate cancer death. Factors associated with metastatic disease progression were identified using Cox regression models.

Results: Of the 32,643 men with non-metastatic prostate cancer at diagnosis 43.1% had localised disease, 5.1% had regional spread and 51.9% had unknown stage. After a median of 6.8 years of follow-up 6708 cases (20.6%) had developed distant metastases. The risk of developing metastatic disease was significantly higher for those with regional (adjusted HR = 2.65, 95% CI: 2.40–2.93) or unknown initial stage (adjusted HR = 1.70, 95% CI: 1.61–1.80), for older men (65–74 years: HR = 1.43, 95% CI: 1.33–1.53; >74 years: HR = 2.73, 95% CI: 2.55–2.93), and those living in inner regional (HR = 1.11, 95% CI: 1.04–1.18) or rural areas (HR = 1.24, 95% CI: 1.14–1.36) or more disadvantaged areas (middle tertile: HR = 1.09, 95% CI: 1.02–1.16; most disadvantaged: HR = 1.12, 95% CI: 1.04–1.19). The risk of developing metastatic disease decreased over calendar time (adjusted HR = 0.98, 95% CI: 0.97–0.99 per year).

Conclusions: After a median follow-up of 6.8 years more than 1 in 5 men diagnosed with non-metastatic prostate cancer developed distant metastases. This estimate of the overall risk of developing metastatic disease in the population, and the geographical disparities identified, can inform the planning of required cancer services.

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1. Introduction

Prostate cancer is the most common cancer diagnosed in Australia (excluding non-melanoma skin cancers), and the second most common cause of cancer death in men [1]. With growing numbers of men diagnosed and living with prostate cancer the health care demands of men with this disease will increase substantially, resulting in a growing burden on the Australian health care system [2]. Information on the risk of developing metastatic disease is needed to provide realistic estimates of prevalent cases requiring follow-up and active treatment [2]. Understanding this risk and the patterns of progression will help inform future effective health service planning.

The majority of men diagnosed with prostate cancer are detected at an early stage, and while localised prostate cancers are believed to have an indolent course, local progression and distant metastasis can develop over the long term [3]. The proportion of men who progress to metastatic disease is not well documented, and only a few studies have examined clinical metastatic progression in

Abbreviations: NSW, New South Wales; CCR, Central Cancer Registry; SES, socio-economic status; ASIR, age-standardised incidence rate; LGA, local government area; ASCC, Australian Standard Geographic Classification; IRSD, Index of Relative Socio-economic Disadvantage; PSA, prostate-specific antigen; HR, hazard ratio; CI, confidence interval.

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selected cases [3,4] or after a single specified treatment in single institutions or selected groups [4–7]. A new method using population-based cancer registry data or routinely collected health data to estimate rates of progression to metastatic breast cancer was described by Lord et al. [8], but to our knowledge there have not yet been any population-wide studies that describe and quantify prostate cancer progression to subsequent metastatic disease after sufficient follow-up.

In this study we used population-based cancer registry data to describe the patterns of progression to metastatic disease in men resident in NSW who had an initial diagnosis of non-metastatic prostate cancer.

2. Materials and methods

This study was approved by the NSW Population and Health Services Research Ethics Committee in April 2009 (Reference: HREC/09/CIPHS/16).

2.1. Data sources

Data for all primary non-metastatic prostate cancer cases (ICD-O-3 C61) [9] diagnosed from 1993 to 2002 were obtained from the New South Wales (NSW) Central Cancer Registry (CCR). NSW is the most populous state in Australia with almost one-third of the total national population [10]. The CCR is the only Australian population-based cancer registry that routinely records summary stage of disease. According to the NSW Health policy directive, if a patient presents for a consultation or treatment at any facility in NSW and has a diagnosis of cancer then the CCR must be notified [11]. The stepwise inclusion and exclusion of patients for analysis is illustrated in Fig. 1. Excluded cases comprised those that were notified post-mortem or through death certificate only, cases that were initially diagnosed with distant metastatic disease, cases that died within four months of initial diagnosis so that we were thus unable to determine their initial stage at diagnosis and cases that were aged 90 years or older at diagnosis (due to the unreliable ascertainment of cause of death for very elderly patients). This resulted in a total of 32,643 non-metastatic prostate cancer cases being included. This cohort of cases was then followed-up for a notification of distant metastatic progression or prostate cancer death to the end of 2007.

2.2. Summary stage of disease

Stage of disease was identified at two time points in the course of the prostate cancer: initial stage at diagnosis was determined based on the highest stage of disease reported within four months of the initial diagnosis, and subsequent metastatic disease was determined by notifications dated more than four months after the initial diagnosis. The summary stage of disease provided by the CCR was based on the stage information available from statutory notification forms, including hospital notifications and pathology reports. Using a modified summary classification [12] that is similar to that used by SEER [13], the CCR classifies stage of disease as: localised (cancer contained entirely in the prostate gland), regional (cancer extended into tissues surrounding the prostate or to regional lymph nodes), distant (cancer extended beyond regional lymph nodes, to bones or to other distant sites) and “unknown” (where information in the notifications was insufficient for the cancer registry to assign stage). As a previous study provided evidence that prostate cancer cases with “unknown” stage at diagnosis differed from those with known stage and so excluding cases with “unknown” stage could therefore cause bias [14], cases with “unknown” stage were included in this study as a separate stage category.

2.3. Study endpoints

Metastatic disease progression was identified by subsequent metastatic disease episode notifications (hereafter referred to as “episode notified” cases), or by notifications of prostate cancer death (hereafter referred to as “prostate cancer death notified” cases). As distant metastatic disease progression is considered to be on the pathway to prostate cancer death, we assumed that men developed metastases at some time before prostate cancer death [4,5]. As information up to four months after diagnosis was used by the CCR to determine cancer stage at diagnosis, the time to metastatic disease notification was calculated from the date four months after prostate cancer diagnosis to either the earliest date of subsequent metastatic notification, or to the date of prostate cancer death, if it occurred more than four months after initial diagnosis [15]. Survival status and the cause of death to the end of 2007 were obtained from the CCR by matching cancer cases against death records from the State Registry of Births, Deaths, and Marriages and the National Death Index. Those who were not recorded as having developed metastatic disease were censored at the date of death from other causes or 31st December 2007 if they were still alive.

2.4. Study variables

Variables used in this analysis included stage of disease at diagnosis, age at diagnosis, year of diagnosis, geographical location, socio-economic status (SES) and age-standardised prostate cancer incidence rate (ASR) by local government area (LGA) of residence at diagnosis. Geographical location of residence at diagnosis was categorised into major cities, inner regional, rural (including outer regional, remote and very remote areas) using the Australian Standard Geographic Classification (ASGC) Remoteness Structure [16]. This Remoteness Structure is recognised as a nationally consistent measure of geographic remoteness, based on the physical road distance to the nearest town or service centre. Index of Relative Socio-economic Disadvantage (IRSD), derived from the 2001 Census, was used as a measure of area-level socio-economic status (SES) [17].

Fig. 1. Inclusion and exclusion of prostate cancer patients in NSW 1993–2002, Australia.
This study cohort included men diagnosed with prostate cancer during the years in which prostate-specific antigen (PSA) testing was introduced and became widespread in Australia. As cases of asymptomatic disease diagnosed through PSA testing may be less likely to progress than other cases, the level of PSA testing in a population could affect the overall risk of disease progression. Data on PSA testing prevalence were not available at either the individual or area level. It has, however, been found that the number of PSA tests conducted within a population is highly correlated with the number of new prostate cancer cases diagnosed in the population \[18,19\]. Thus, in the absence of data on small area PSA testing rates, we instead used the 5-year period ASR for each LGA as a marker for the rate of PSA testing. For each LGA in NSW, ASRs and IRSD scores were ranked and then grouped into three levels (high, medium and low) with the similar sized populations in each group.

2.5. Statistical analysis

To describe the patterns of disease progression of prostate cancer from non-metastatic to metastatic disease, the Kaplan–Meier method was used to estimate the cumulative incidence rate and the log-rank test was used to test for differences in time to metastatic prostate cancer by initial stage at diagnosis. The annual metastatic prostate cancer hazard as the rate of failure within one-year intervals by initial stage at diagnosis was graphically represented using gauze kernel smooth. Cox proportional hazard regression models were used to identify risk factors associated with progression to metastatic disease. We estimated median survival after a notification of metastatic disease to provide further information about the potential issue of cases living with metastatic prostate cancer that was not notified to the CCR. Testing of the interaction of the variables included in the regression with survival time, and visual inspection of the Schoenfeld and scaled Schoenfeld residuals, indicated that the proportional hazards assumption was satisfied \[20\]. All analyses were performed using STATA (version 13.1, STATA Corporation, College Station, TX).

3. Results

Of the 32,643 men with non-metastatic prostate cancer at diagnosis, 43.1% had localised disease, 5.1% regional spread and 51.9% had unknown stage of disease (Table 1). The median age at diagnosis was 70 years, and two-thirds of patients were resident in major cities at the time of initial diagnosis. After a median of 6.8 years (range: 0.1 to 14.7 years) of follow-up, a total of 6708 cases (20.6%) had developed subsequent distant metastases. Of these, 63.4% were identified by metastatic episode notifications and 36.6% were identified by prostate cancer death. The overall median time to notification of metastatic disease was 3.6 years. The median survival after a notification of metastatic prostate cancer was 6 months.

Cases with regional or unknown stage at diagnosis had higher cumulative incidence of metastatic disease than those with localised disease (logrank test \(p < 0.0001\), Fig. 2). The 10-year cumulative incidence rates for cases with localised, regional and unknown stage at diagnosis were 17.1, 33.9, and 30.8% respectively. For all initial stages, the trends in the cumulative incidence of metastatic disease appeared to be still increasing after 14 years of follow-up.

Fig. 3 shows the trends for the annual hazard for progression to metastatic disease by the number of years of follow-up. We found that the annual hazards for cases with regional and “unknown” stage were higher than those with localised initial stage of disease. Over time the hazard of developing metastatic disease for cases with unknown initial stage decreased continuously and appeared

| Table 1 | Baseline characteristics of men with non-metastatic prostate cancer by stage at initial diagnosis in New South Wales, Australia 1993–2002. |
|---|---|---|---|
| Characteristics | Stage at diagnosis | Total number of cases | Metastatic progression |
| | Localised | Regional | Unknown* | n (% within categories) | n (% within total) | % within categories |
| **Age at diagnosis (Years)** | | | | | | |
| Mean (Standard deviation) | 68.2 (8.5) | 65.6 (8.5) | 71.7 (8.2) | 69.3 (8.6) | | |
| **Year of diagnosis** | | | | | | |
| 1993–1997 | 7075 (42.2) | 752 (4.5) | 8944 (53.3) | 16768 (51.4) | 24.5 |
| 1998–2002 | 6985 (44.0) | 907 (5.7) | 7983 (50.3) | 15875 (48.6) | 16.4 |
| **Geographical location** | | | | | | |
| Major cities | 10,121 (45.5) | 1162 (5.2) | 10953 (49.3) | 22236 (68.1) | 19.7 |
| Inner regional | 2957 (38.1) | 348 (4.5) | 4466 (57.5) | 7771 (23.8) | 21.9 |
| Rural | 982 (37.3) | 149 (5.7) | 1505 (57.1) | 2636 (8.1) | 23.9 |
| **Socio-economic status** | | | | | | |
| Least disadvantaged | 5413 (48.4) | 681 (6.1) | 5101 (45.6) | 11195 (34.3) | 18.2 |
| Middle tertile | 4525 (41.0) | 499 (4.5) | 6001 (54.4) | 11025 (33.8) | 21.4 |
| Most disadvantaged | 4122 (39.6) | 479 (4.6) | 5822 (55.9) | 10423 (31.9) | 22.1 |
| **Prostate cancer incidence rate** | | | | | | |
| Lowest tertile | 3232 (40.6) | 357 (4.5) | 4369 (54.9) | 7958 (24.4) | 21.6 |
| Middle tertile | 4355 (39.9) | 502 (4.6) | 6052 (55.5) | 10909 (33.4) | 21.7 |
| Highest tertile | 6473 (47.0) | 800 (5.8) | 6503 (47.2) | 13776 (42.2) | 19.1 |
| **Metastatic disease progression** | | | | | | |
| No | 12,057 (46.5) | 1163 (4.5) | 12,715 (49.0) | 25,935 (79.5) | | |
| Yes | 2003 (29.9) | 496 (7.4) | 2409 (62.8) | 6708 (20.6) | | |
| Episode notified | 1321 (31.1) | 313 (7.4) | 2621 (61.6) | 4255 (13.0) | | |
| Prostate cancer death notified | 682 (27.8) | 183 (7.5) | 1588 (64.7) | 2453 (7.5) | | |
| Total | 14,080 (43.1) | 1659 (5.1) | 16,924 (51.9) | 32,643 (100.0) | 20.6 |

* Unknown stage recorded by the NSW Central Cancer Registry.

**Geographical location and socio-economic status were based on the man’s place of residence at diagnosis.

Age-standardised prostate cancer incidence rate by 5-year period in Local Government Area of the man’s residence, standardised to 2001 Australian standard population.

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to converge with that of cases originally diagnosed as localised stage.

In a multivariable analysis (Table 2), the risk of developing metastatic disease was significantly increased for those with regional (HR = 2.65, 95% CI: 2.40–2.93) or unknown initial stage (HR = 1.70, 95% CI: 1.61–1.80), for cases diagnosed at an older age (65–74 years: HR = 1.43, 95% CI: 1.33–1.53; >74 years: HR = 2.73, 95% CI: 2.55–2.93), those living in inner regional (HR = 1.11, 95% CI: 1.04–1.18) or rural areas (HR = 1.24, 95% CI: 1.14–1.36), and those living in more disadvantaged areas (middle tertile: HR = 1.09, 95% CI: 1.02–1.16; most disadvantaged: HR = 1.12, 95% CI: 1.04–1.19). The risk of developing metastatic disease decreased with year of diagnosis (HR = 0.98, 95% CI: 0.97–0.99 per year) and medium or high age-standardised prostate cancer incidence rate (middle tertile: HR = 0.91, 95% CI: 0.85–0.97; highest tertile: HR = 0.85, 95% CI: 0.79–0.90).

4. Discussion

To our knowledge, this is the first population-based study to examine the patterns of prostate cancer progression from non-metastatic to metastatic disease. After a median follow-up of 6.8 years more than 1 in 5 men initially diagnosed with non-metastatic prostate cancer developed distant metastases. As NSW is the most populous state in Australia, with almost one-third of the total national population [10], and has cancer mortality rates that are almost identical to the national rates [1], we believe that our results may be generalised to the whole Australian population.

Table 2

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total number of cases (% of Metastatic progression)</th>
<th>Bivariable model</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
<th>Multivariable modela</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td><strong>Stage at diagnosis</strong></td>
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<td></td>
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<tr>
<td>Localised</td>
<td>14,060 (14.2)</td>
<td>1.00</td>
<td></td>
<td>(2.09–2.55)</td>
<td>&lt;0.0001</td>
<td></td>
<td>1.00</td>
<td>(2.40–2.93)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Regional</td>
<td>1659 (29.9)</td>
<td>2.31</td>
<td>(1.92–2.13)</td>
<td></td>
<td>&lt;0.0001</td>
<td></td>
<td>2.65</td>
<td>(1.61–1.80)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Unknownb</td>
<td>16,924 (24.9)</td>
<td>1.00</td>
<td></td>
<td>(1.39–1.59)</td>
<td>&lt;0.0001</td>
<td></td>
<td>1.00</td>
<td>(1.33–1.53)</td>
<td>&lt;0.0001</td>
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<td><strong>Age at diagnosis</strong></td>
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<tr>
<td>&lt;65 years</td>
<td>8466 (14.2)</td>
<td>1.00</td>
<td></td>
<td>(2.76–3.16)</td>
<td>&lt;0.0001</td>
<td></td>
<td>1.43</td>
<td>(2.55–2.93)</td>
<td>&lt;0.0001</td>
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<tr>
<td>65–74 years</td>
<td>14,106 (19.6)</td>
<td>1.48</td>
<td>(1.97–2.59)</td>
<td></td>
<td>&lt;0.0001</td>
<td></td>
<td>2.73</td>
<td>(1.92–2.13)</td>
<td>&lt;0.0001</td>
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<tr>
<td>&gt;74 years</td>
<td>10,071 (27.2)</td>
<td>1.48</td>
<td>(1.10–1.23)</td>
<td></td>
<td>&lt;0.0001</td>
<td></td>
<td>1.11</td>
<td>(1.04–1.18)</td>
<td>&lt;0.0001</td>
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<td><strong>Year of diagnosis</strong></td>
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<td>One year increase</td>
<td>9.07 (19.7)</td>
<td>0.97</td>
<td>(0.96–0.98)</td>
<td></td>
<td>&lt;0.0001</td>
<td></td>
<td>0.98</td>
<td>(0.97–0.99)</td>
<td>&lt;0.0001</td>
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<tr>
<td><strong>Geographical location</strong></td>
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<tr>
<td>Major cities</td>
<td>22,236 (19.7)</td>
<td>1.00</td>
<td></td>
<td>(1.10–1.23)</td>
<td>&lt;0.0001</td>
<td></td>
<td>1.00</td>
<td>(1.04–1.18)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Inner regional</td>
<td>7771 (21.9)</td>
<td>1.16</td>
<td>(1.20–1.42)</td>
<td></td>
<td>&lt;0.0001</td>
<td></td>
<td>1.11</td>
<td>(1.14–1.36)</td>
<td>0.004</td>
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<tr>
<td>Rural</td>
<td>2636 (23.9)</td>
<td>1.30</td>
<td>(1.16–1.31)</td>
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<td>&lt;0.0001</td>
<td></td>
<td>1.24</td>
<td>(1.00–1.16)</td>
<td>&lt;0.0001</td>
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<td><strong>Socio-economic status</strong></td>
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<tr>
<td>Least disadvantaged</td>
<td>11,195 (18.2)</td>
<td>1.00</td>
<td></td>
<td>(1.12–1.37)</td>
<td>&lt;0.0001</td>
<td></td>
<td>1.09</td>
<td>(1.12–1.19)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Middle tertile</td>
<td>11,025 (21.4)</td>
<td>1.23</td>
<td>(1.00–1.16)</td>
<td></td>
<td>&lt;0.0001</td>
<td></td>
<td>1.12</td>
<td>(1.04–1.19)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Most disadvantaged</td>
<td>10,423 (22.1)</td>
<td>1.12</td>
<td>(0.89–1.01)</td>
<td></td>
<td>&lt;0.0001</td>
<td></td>
<td>0.91</td>
<td>(0.85–0.97)</td>
<td>&lt;0.0001</td>
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<tr>
<td><strong>Prostate cancer incidence</strong></td>
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<tr>
<td>Lowest tertile</td>
<td>7958 (21.6)</td>
<td>1.00</td>
<td></td>
<td>(0.78–0.89)</td>
<td>&lt;0.0001</td>
<td></td>
<td>1.00</td>
<td>(0.79–0.90)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Middle tertile</td>
<td>10,909 (21.7)</td>
<td>0.83</td>
<td>(0.85–0.97)</td>
<td></td>
<td>&lt;0.0001</td>
<td></td>
<td>0.85</td>
<td>(0.85–0.97)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Highest tertile</td>
<td>13,776 (21.1)</td>
<td>0.83</td>
<td>(0.85–0.97)</td>
<td></td>
<td>&lt;0.0001</td>
<td></td>
<td>0.85</td>
<td>(0.85–0.97)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

a Adjusted hazard ratio from multivariable model including all variables listed in the table.
b Unknown stage recorded by the NSW Central Cancer Registry.
c Geographical location and socio-economic status were based on the man’s place of residence at diagnosis.
d Age-standardised prostate cancer incidence rate by 5-year period in Local Government Area of the man’s residence, standardised to 2001 Australian standard population.

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and to other countries with similar health care systems. We found that men with regional or “unknown” initial stage, those aged 65 years and older at diagnosis, men living in inner regional or rural areas, and those living in disadvantaged areas were at greater risk of progressing to metastatic prostate cancer than other men.

Previous international studies have reported a wide range in rates of progression to metastatic prostate cancer, with the variation likely to be due to the selection of cases, different lengths of follow-up, and in some cases, a focus on progression after a single specified treatment. The rate of progression to metastatic disease we observed (20.6%) was higher than the rate (12.8%) from a single county cancer registry in the USA (Seattle, Washington) [4]. This difference may be due to the younger age of the men in the USA study (median age 58 years), or because metastatic progression was self-reported in the American study. A study from Sweden reported a slightly lower rate of metastatic progression (18.4%) in localised prostate cancer cases diagnosed in the period prior to the introduction of PSA testing (mean age 72 years, mean time to metastatic progression 9.2 years) [3]. Other studies [5–7] have tended to focus on rates of metastatic progression after patients in a single institution have received specific treatments, and have generally reported a wide range of metastatic progression rates (3.4–21.0%) due to the selection of cases from low-risk or high-risk groups. The rate of progression after long-term follow up that we reported was an overall estimate for the population of cases with non-metastatic prostate cancer regardless of the treatment received, so it is difficult to compare results from these studies.

Our study found that men with “unknown” stage at diagnosis recorded in the CCR had a significantly higher risk of developing metastatic disease than those initially diagnosed with localised stage, but a lower risk than those initially diagnosed with regional disease. This pattern of progression to metastatic disease by initial stage at diagnosis is consistent with the pattern observed for prostate cancer specific survival, and confirms that the cases with “unknown” stage at diagnosis recorded in the CCR are likely to actually be a mixture of stages [14]. National and international data does, however, suggest that the proportion of prostate cancer cases initially diagnosed with metastatic disease is generally very low. The USA SEER Cancer Statistics Review reported that in the period 1992–2001 5–6% of all prostate cancer cases were initially diagnosed with distant stage (3–4% for men aged less than 65 years) [21]. As the use of PSA testing is similarly high in men in the USA and Australia [22], we may expect a similar stage distribution for prostate cancer in the two populations, with only a very low proportion of prostate cancer cases initially diagnosed with metastatic disease. This pattern is generally confirmed by the results of the population-based NSW Prostate Cancer Care and Outcome Study (PCOS) of men aged up to 70 years diagnosed in 2000–2002. In PCOS 12% of cases were initially diagnosed with non-localised disease [23], and only 3.8% of all prostate cancer cases were diagnosed with distant stage (unpublished data). As previously noted, in our study population, 5.2% of all prostate cancer cases were excluded as they were initially diagnosed with distant metastasis, so it is unlikely that a large proportion of the group with “unknown” stage had metastatic disease at diagnosis. Therefore, we would expect the effect of possible misclassification of metastatic prostate cancer in the group with “unknown” stage to be minimal. In addition, the men with more aggressive prostate cancer were likely to develop metastatic disease or die in the early years of follow-up, so that in the later years of follow-up the remaining patients would mainly be those with localised disease. This may explain the apparent convergence of the annual hazard rate for the group with “unknown” stage towards that for localised stage as observed in this study.

We also found evidence that the risk of progressing to metastatic prostate cancer was significantly higher for men living in inner regional or rural areas than for those living in major cities, and higher for men living in areas of low SES compared to men in areas of high SES. A previous study using linked cancer registry and hospital records found that men living in rural NSW or in areas of low SES were less likely to receive a radical prostatectomy than those in urban or high SES areas [24]. The higher risk of progression to metastatic prostate cancer observed for men living in inner regional, rural or more disadvantaged areas may be partly attributed to differences in patterns of care due to difficulties associated with the access and provision of cancer services. The geographical variation in the risk of progression to metastatic prostate cancer is consistent with that reported in a previous study in survival differences by geographical location and SES [25].

As this study cohort included prostate cancer patients diagnosed in the period in which PSA testing was introduced and became widespread in Australia, it is possible that men living in areas with high PSA testing rates were more likely to be diagnosed with low-risk cancers identified through PSA testing, and in turn were at lower risk of developing metastatic disease. To control this possibility we used the age-standardised prostate cancer incidence rate as a marker for PSA testing activity, and found that cases in areas with higher incidence rates were less likely to develop metastatic disease.

Although prostate cancer is generally a relatively slow-growing cancer, distant metastases can develop over the long term, even among patients considered to have low risk at diagnosis [3]. Our study found continuously increasing trends in the cumulative incidence rates of metastatic disease progression for all initial stages of prostate cancer. A follow-up period of at least 15 years is necessary when investigating patterns of metastatic disease progression, as this allows for the identification of cases experiencing late progression, which is not a rare event. For this reason population-based studies are considered to be a cost-effective method for investigating prostate cancer metastatic disease progression and can provide useful information for planning prostate cancer services and surveillance management.

This study has some limitations. Although the accuracy of the CCR data on primary cancer events is known to be high [26], the completeness and accuracy of subsequent metastatic disease notifications have not been formally investigated. It is therefore possible that due to the issue of incomplete episode data the rate of progression to metastatic disease found in this study is an underestimate of the true rate [27,28]. However, as prostate cancer death was included as one source of information on disease progression this possible under-estimation should be minimised. Previous research suggests that the recording of data on cancer deaths is very complete at the CCR and that cause of death is well ascertained [29,30]. Given that the median survival after a notification of metastasis was low (6 months), we believe that the number of men living with metastatic prostate cancer who were not notified to the CCR or died from prostate cancer after disease progression is likely to be small. Another limitation is the possibility of misclassification of initial stage. Fortunately the effect of such misclassification appears to be minimal, as it is suggested that the proportion with metastatic disease at diagnosis is low and they were excluded from the analysis. The results may also be limited because only an area-level indicator of SES based on the man’s place of residence was available and some individuals may have been misclassified. However, a number of studies have demonstrated the importance of area-level socio-economic indicators in measuring health inequalities in Australia [31] and in the USA [32], indicating that this method is sufficiently robust in these circumstances.

The study has many strengths, as we have undertaken a statewide population-based study adopting a method using routinely collected cancer registry data [8], which is more
representative and comprehensive than any previous study on this topic. Furthermore, this method provided long-term follow-up of cases, so that we were able to assess the progression of prostate cancer to metastatic disease over an extended time period, and we used clinical progression to metastatic disease as the endpoint rather than biochemical failure, recognising that biochemical failure has limitations in predicting prostate cancer death [4,33]. Our methods may be applicable elsewhere and could help to increase the utilisation of data from other cancer registries.

In conclusion, the rate of progression to metastatic prostate cancer estimated in this statewide population-based study provides important and previously unavailable information on patient outcomes over an extended time period. The continuously increasing trends in metastatic disease progression each year up to 14 years of follow-up confirmed that distant metastasis can develop over the long term, and the estimated overall risk of developing metastatic disease in the population should help to inform health services planning. Moreover, the disparities identified in the progression to metastatic disease based on accessibility to health care suggest that the development of future cancer care services could be better targeted to areas of need.

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**Conflicts of interests**

The authors declare that they have no conflicts of interest.

**Authorship Contribution**

QL designed the study with inputs from XQY and DOC. QL performed the statistical analysis and drafted the manuscript. DOC and XQY guided the analysis and helped to revise the manuscript. DS helped to interpret the results and revise the manuscript. All authors read and approved the final manuscript.

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