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

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ABSTRACT

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.

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; ASR, age-standardised incidence rate; LGA, local government area; ASGC, 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 assignation 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.

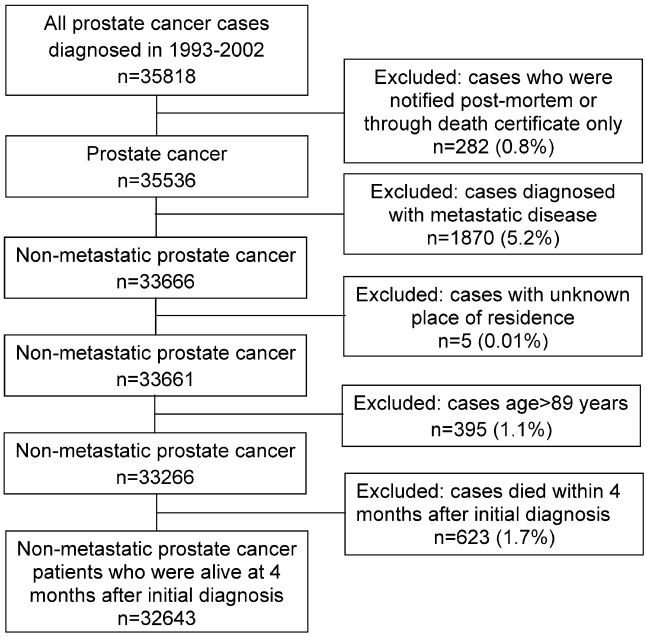

Fig. 1. Inclusion and exclusion of prostate cancer patients in NSW 1993–2002, Australia.

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].