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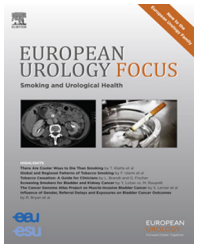


Epidemiology

# Past, Current, and Future Incidence Rates and Burden of Metastatic Prostate Cancer in the United States

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## Abstract

***Background:*** Metastatic prostate cancer (PCA) remains a highly lethal malignancy in the USA. As prostate-specific antigen testing declines nationally, detailed assessment of current age- and race-specific incidence trends and quantitative forecasts are needed.
***Objective:*** To evaluate the current trends of metastatic PCA by age and race, and forecast the number of new cases (annual burden) and future trends.
***Design, setting, and participants:*** We derived incidence data for men aged ≥45 yr who were diagnosed with metastatic PCA from the population-based Surveillance, Epidemiology, and End Results registries.
***Outcome measurements and statistical analysis:*** We examined the current trends of metastatic PCA from 2004 to 2014, and forecast the annual burden and incidence rates by age and race for 2015–2025, using age–period–cohort models and population projections. We also examined alternative forecasts (2012–2025) using trends prior to the revised screening guidelines issued in 2012.
***Results and limitations:*** Metastatic PCA, steadily declining from 2004 to 2007 by 1.45%/yr, began to increase by 0.58%/yr after 2008, which accelerated to 2.74%/yr following the 2012 United States Preventive Services Task Force recommendations—a pattern that was magnified among men aged ≤69 yr and white men. Forecasts project the incidence to increase by 1.03%/yr through 2025, with men aged 45–54 yr (2.29%/yr) and 55–69 yr (1.53%/yr) increasing more rapidly. Meanwhile, the annual burden is expected to increase 42% by 2025. Our forecasts estimated an additional 15 891 metastatic cases from 2015 to 2025 compared with alternative forecasts using trends prior to 2012.
***Conclusions:*** The recent uptick in metastatic PCA rates has resulted in forecasts that project increasing rates through 2025, particularly among men aged ≤69 yr. Moreover, racial disparities are expected to persist and the annual burden will increase considerably. The impact of the prior and current PCA screening recommendations on metastatic PCA rates requires continued examination.
***Patient summary:*** In this report, we assessed how the incidence of metastatic prostate cancer has changed over recent years, and forecast future incidence trends and the number of new cases expected each year. We found that the incidence of metastatic prostate cancer has been increasing more rapidly since 2012, resulting in a rise in both future incidence and the number of new cases by 2025. Future incidence rates and the number of new cases were reduced in alternative forecasts using data prior to the 2012 United States Preventive Services Task Force (USPSTF) recommendations against prostate-specific antigen (PSA) testing for prostate cancer. There is a need for additional research that examines whether national declines in PSA testing contributed to increases in rates of metastatic disease. The incidence of metastatic disease in black men is still expected to occur at considerably higher rates compared with that in white men.


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## 1. Introduction

Prostate cancer (PCA) is the most frequently diagnosed cancer among men in the USA, with an estimated 161 360 new cases expected in 2017 [1]. After widespread adoption of prostate-specific antigen (PSA) testing in the USA in the late 1980s [2], overall PCA incidence rates doubled followed by a subsequent decline and recent stabilization [3]. Approximately 6% of new PCA cases present with metastatic disease, with a 5-yr survival rate of only 29% [4]. Metastatic PCA often becomes androgen independent, which contributes to its poor prognosis [5]. No improvement has been noted in overall or cause-specific survival for men presenting with metastatic PCA over the last 2 decades [6]. The incidence of metastatic PCA is of great interest, given that this form of the disease is less amenable to treatment and effective screening should identify tumors that are destined to metastasize at earlier localized/regional stages [7,8].

Whether recent trends of metastatic PCA have been increasing is controversial. Recent research has reported an increasing incidence of metastatic PCA based on relative increases in the absolute number of new cases [9], while other studies have suggested a recent stabilization [7,10,11] or increases among older men [12]. Whether the incidence of metastatic PCA is increasing is important, as declines have been a major contributor to the reductions observed in PCA mortality [13]. In addition, following the US Preventative Services Task Force (USPSTF) guidelines in 2008 and 2012, which advised against routine PSA testing for PCA—first in 2008 among men aged $\geq$75 yr and then in 2012 among men of all ages [14], a recent decline of approximately 20–30% in relative PSA testing rates has been observed from 2010 to 2013 [15,16]. Whether recent decreases in PSA testing rates have influenced current incidence trends in metastatic PCA [17] or could influence future trends remains open to debate.

There is an urgent need to accurately assess recent incidence trends of metastatic PCA, particularly by age and race/ethnicity, as disparities have not been fully characterized. Short-term forecasts could aid in quantifying the burden of metastatic cases projected over the next decade. Therefore, in this study, we assess current incidence trends of metastatic PCA by age and race/ethnicity, and forecast incidence rates and annual burden (number of new cases) of metastatic PCA in the USA through 2025, using population-based cancer surveillance data and national population projections.

## 2. Patients and methods

We obtained single-year PCA case counts and population estimates for men aged 45–94 yr at diagnosis from 18 of the Surveillance, Epidemiology, and End Results (SEER) registry databases (2004–2014), covering 28% of the US population [18]. In addition to the single-year population estimates available for men aged 45–84 yr in SEER, single-year race-specific population estimates for men aged 85–94 yr were obtained from intercensal (for July 1, 2000–2014) files provided by the National Center for Health Statistics and U.S. Census Bureau's Population Estimates Program.

Primary malignant prostate tumors were defined by International Classification of Diseases for Oncology, Third Edition, using topography code C619. SEER collaborative staging was used to select cases with metastatic disease at initial clinical presentation and those that were pathologically confirmed. Individuals with unknown age at diagnosis were excluded ($N = 2$), as were men whose diagnosis was based solely on autopsy or death certificates ($N = 33$).

The US Census Bureau projected population estimates for the entire USA stratified by age (single years), sex, race, and Hispanic ethnicity through 2060 [19]. These projections are based on 2013 population estimates and assumptions about future deaths, births, and net international migration. We categorized race/ethnicity as non-Hispanic white (white), non-Hispanic black (black), non-Hispanic Asian (Asian), or all races of Hispanic ethnicity (Hispanic).

### 2.1. Statistical analysis

Our forecasting method applied age–period–cohort (APC) models to estimate future age- and race-specific incidence rates and 95% confidence intervals [20]. APC models enabled us to distinguish between influences that occurred in specific time periods for all age groups (period effects) versus effects associated with specific birth cohorts (generational effects) [21]. The detailed methodology for the APC models and forecasting has been described previously [22]. Future estimated incidence rates were obtained by multiplying the observed and estimated age-specific rates in a referent birth cohort by the rate ratio of each successive birth cohort to the original, fixed referent birth cohort. As each birth cohort ages into PSA-based screening ranges, the APC models are uniquely tailored to forecast race- and age-specific rates, which should reflect different screening patterns in each subgroup. Forecast rates were obtained by extrapolating the observed age-specific birth-cohort rate ratios using a joinpoint piecewise log-linear regression model [23]. The goodness of fit of underlying APC models was evaluated based on the degree of the overdispersion, normality of the residuals, and how closely fitted rates matched the observed rates.

We calculated age-standardized and age-specific incidence rates per 100 000 person years, and race-specific rate ratios to examine racial disparities by time period and age at diagnosis. We calculated annual percentage changes for the observed and forecast rates.

To compute annual burden of metastatic PCA (annual number of new cases), we summed the product of forecast age-specific incidence rates and projected age-specific population sizes [22]. We also estimated the total (cumulative) percentage change in burden from 2015 to 2025.

We examined the impact of whether the recent national declines in PSA testing following the 2012 USPSTF recommendation influenced forecasts in an alternative pre-2012 USPSTF model by restricting the observed period used for forecasting to 2004–2011, and testing for any excess in rates and burden that was observed versus expected in the 3-yr period (2012–2014) following the 2012 USPSTF recommendations.

Statistical analyses were performed in Matlab, version R2016a. All statistical tests were two sided, and $p < 0.05$ was considered statistically significant.

### 2.2. Sensitivity analysis

We further examined the impact of the USPSTF recommendations, and subsequent national PSA testing declines forecasts by forecasting a variation of the main model that included extrapolation of any excess in observed-to-expected rates during 2012–2014.

## 3. Results

For the 25 033 men aged 45–94 yr who were diagnosed with metastatic PCA from 2004 to 2014, the median age at

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