

## ORIGINAL ARTICLE

# Increasing incidence of metastatic prostate cancer in the United States (2004–2013)

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**BACKGROUND:** Changes in prostate cancer screening practices in the United States have led to recent declines in overall incidence, but it is unknown whether relaxed screening has led to changes in the incidence of advanced and metastatic prostate cancer at diagnosis.

**METHODS:** We identified all men diagnosed with prostate cancer in the National Cancer Data Base (2004–2013) at 1089 different health-care facilities in the United States. Joinpoint regressions were used to model annual percentage changes (APCs) in the incidence of prostate cancer based on stage relative to that of 2004.

**RESULTS:** The annual incidence of metastatic prostate cancer increased from 2007 to 2013 (Joinpoint regression: APC: 7.1%,  $P < 0.05$ ) and in 2013 was 72% more than that of 2004. The incidence of low-risk prostate cancer decreased from years 2007 to 2013 (APC:  $-9.3%$ ,  $P < 0.05$ ) to 37% less than that of 2004. The greatest increase in metastatic prostate cancer was seen in men aged 55–69 years (92% increase from 2004 to 2013).

**CONCLUSIONS:** Beginning in 2007, the incidence of metastatic prostate cancer has increased especially among men in the age group thought most likely to benefit from definitive treatment for prostate cancer. These data highlight the continued need for nationwide refinements in prostate cancer screening and treatment.

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## INTRODUCTION

Over the past decade, there has been substantial shifts in PSA screening practices in response to randomized trial data and US Preventive Services Task Force (USPSTF) recommendations in 2008 and 2012.<sup>1,2</sup> This has resulted in reduced screening with associated declines in overall prostate cancer incidence.<sup>3,4</sup> Using data from a large cancer registry from 2004 through 2013, we sought to analyze the temporal relationship between relaxed screening and increases in yearly incidence of advanced or metastatic prostate cancer.

## MATERIALS AND METHODS

From the National Cancer Data Base (NCDB), all men diagnosed with adenocarcinoma of the prostate (International Classification of Diseases for Oncology histology codes 8550 and 8140) from 2004 through 2013 were included. Only patients with data available to risk stratify based on National Comprehensive Cancer Network (NCCN) guidelines were included (low risk: cT1cT2a, PSA  $< 10$  ng ml<sup>-1</sup> and Gleason score  $\leq 6$ ; intermediate risk: cT2b–T2c, PSA 10–20 ng ml<sup>-1</sup> and Gleason score 7; high risk: cT3–4, PSA  $\geq 20$  ng ml<sup>-1</sup> and Gleason score 8–10; metastatic cN1 or cM1).<sup>5</sup> To avoid bias in temporal trends, the analysis was limited to facilities that contributed prostate cancer patient data each year during the study period. After those facilities were excluded, a total of 767 550 patients from 1089 facilities were analyzed.

The primary outcome was annual incidence of prostate cancer based on NCCN risk groups relative to that of 2004. That is, the outcome denominator was the incidence in 2004 and the numerator was the incidence for every year after. Patients were considered to have metastatic prostate cancer if they were found to have clinically nodal or distant metastases (cN1 or cM1) at the time of diagnosis. To model temporal trends in incidence, Joinpoint software 4.2.0.2 (<http://surveillance.cancer.gov/joinpoint/>) was used to estimate annual percent changes (APCs) in incidence relative to 2004 and to identify significant changes in the linear slope of annual prostate cancer incidence stratified by individual risk and age groups. A two-sided  $P < 0.05$  was used to determine whether APCs were statistically significant. The Mann–Whitney  $U$ -test was used to compare annual median diagnostic PSA values among men with metastatic prostate cancer. This study of de-identified, publicly available data was determined to be exempt by the Northwestern University Institutional Review Board.

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## RESULTS

Of the 767 550 men with prostate cancer included in our study, 3% had metastases at diagnosis. The remainder had localized disease: 32% low, 45% intermediate and 20% high risk (Table 1).<sup>5</sup> Relative to 2004, the annual incidence of all prostate cancer did not change significantly over time (Figure 1 and Table 1). The incidence of low-risk prostate cancer decreased from years 2007 to 2013 (Joinpoint regression, APC:  $-9.3%$ ,  $P < 0.05$ ) to 37% less than that of 2004 (25 708 cases in 2004 to 16 223 in 2013). Intermediate-risk prostate cancer increased from 2004 to 2008 (APC: 10.0%,  $P < 0.05$ ) and did not change significantly in the following years (APC  $-2.7%$ ,  $P = 0.3$ ). The incidence of intermediate-risk prostate cancer was 23% more in 2013 compared with 2004. Similarly, the incidence of high-risk prostate cancer rose from 2004 to 2008 and declined thereafter, although these changes were not statistically significant. Conversely, the incidence of metastatic prostate cancer rose from 2007 to 2013 (APC: 7.1%,  $P < 0.05$ ) increasing to 72% more than that of 2004 (1685 cases in 2004 to 2890 in 2013).

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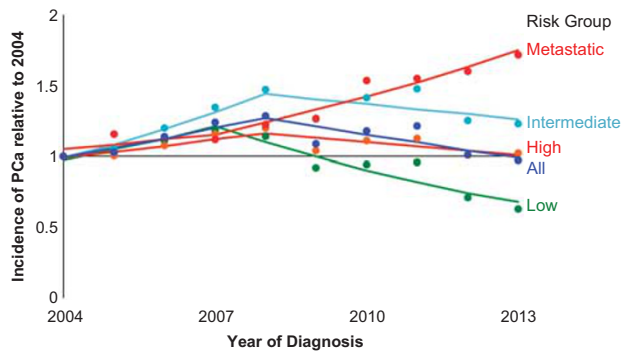
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**Table 1.** Annual incidence of prostate cancer based on National Comprehensive Cancer Network risk group in the National Cancer Data Base

Year of diagnosis	Low risk	Intermediate risk	High risk	Metastatic	All
2004	25 708	27 347	14 074	1685	68 814
2005	25 993	28 761	14 121	1947	70 822
2006	28 509	32 753	15 126	1909	78 297
2007	30 323	36 766	16 256	1884	85 229
2008	29 327	40 201	16 870	2062	88 460
2009	23 643	34 497	14 627	2135	74 902
2010	24 264	38 628	15 630	2584	81 106
2011	24 626	40 394	15 822	2609	83 451
2012	18 284	34 215	14 203	2697	69 399
2013	16 223	33 578	14 379	2890	67 070
Total	246 900	347 140	151 108	22 402	767 550

Annual data are reported from 1089 facilities that contributed prostate cancer patient data during each year of the study period.



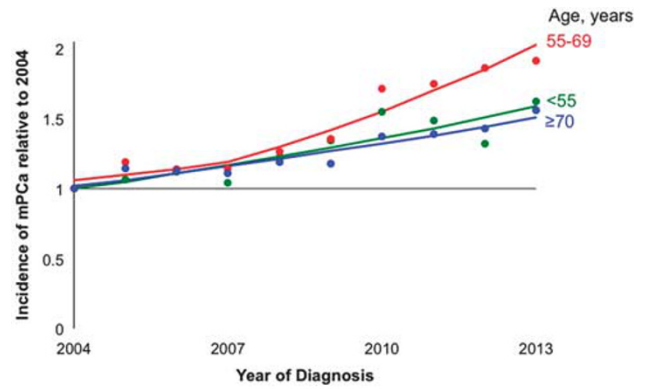
Risk Group	Trend 1			Trend 2		
	Interval	APC	p	Interval	APC	p
Low	2004-2007	7.5	0.3	2007-2013	-9.3	<0.05
Intermediate	2004-2008	10	<0.05	2008-2013	-2.7	0.3
High	2004-2008	4.1	0.1	2008-2013	-2.7	0.1
Metastatic	2004-2007	3.3	0.4	2007-2013	7.1	<0.05
All	2004-2008	6.3	0.1	2007-2013	-4.8	0.1

**Figure 1.** Annual incidence of prostate cancer based on the NCCN risk group relative to 2004 in the United States. Joinpoint regressions were used to model linear trends and determine statistical significance. Trend 1 represents an initial best fit line, whereas trend 2 represents a second linear fit if there is a change in trend from the initial line. The incidence of metastatic prostate cancer has increased recently by 72%, whereas the incidence of low-risk prostate cancer decreased by 37%. APC, annual percentage change; NCCN, National Comprehensive Cancer Network; PCa, prostate cancer.

The increasing incidence of metastatic prostate cancer was statistically significantly in all age groups with the largest increase seen in men aged 55 to 69 years from 702 cases in 2004 to 1345 in 2013 (92% increase; Figure 2 and Table 2). Whereas median PSA levels among men diagnosed with localized disease were stable over the study period (6.1 ng ml<sup>-1</sup> (interquartile range (IQR) 4.5–9.6 ng ml<sup>-1</sup>) to 6.2 ng ml<sup>-1</sup> (IQR 4.6–9.6 ng ml<sup>-1</sup>)), the median PSA levels among men with metastatic prostate cancer increased from 25.5 ng ml<sup>-1</sup> (IQR 10.4–67.5 ng ml<sup>-1</sup>) in 2004 to 49.7 ng ml<sup>-1</sup> (IQR 14.3–98.0 ng ml<sup>-1</sup>) in 2013 (*P* < 0.001).

**DISCUSSION**

Since 2007, the incidence of metastatic prostate cancer has risen significantly whereas that of low-risk prostate cancer has simultaneously fallen. The largest increase in metastatic prostate



Age, years	Trend 1			Trend 2		
	Interval	APC	p	Interval	APC	p
<55	2004-2013	5.3	<0.05			
55-69	2004-2007	4	0.5	2007-2013	9.3	<0.05
≥70	2004-2013	4.5	<0.05			

**Figure 2.** Annual incidence of metastatic prostate cancer based on age relative to 2004 in the United States. Joinpoint regressions were used to model linear trends and determine statistical significance. Trend 1 represents an initial best fit line, whereas trend 2 represents a second linear fit if there is a change in trend from the initial line. The incidence of metastatic prostate cancer has increased recently in all age groups, with the largest increases seen in men aged 55–69 (92%) years. APC, annual percentage change; mPCa, metastatic prostate cancer.

**Table 2.** Annual incidence of metastatic prostate cancer based on age in the National Cancer Data Base

Year of diagnosis	< 55	55–69	≥ 70	All
2004	166	702	817	1685
2005	177	836	934	1947
2006	186	800	923	1909
2007	173	804	907	1884
2008	203	888	971	2062
2009	223	951	961	2135
2010	257	1205	1122	2584
2011	247	1229	1133	2609
2012	219	1308	1170	2697
2013	269	1345	1276	2890
Total	2120	10 068	10 214	22 402

Annual data are reported from 1089 facilities that contributed prostate cancer patient data during each year of the study period.

cancer was seen among the age group (55–69 years) thought to benefit most from prostate cancer screening and early definitive treatment.<sup>6</sup> These findings cannot be explained completely by reactions to the USPSTF recommendations alone, as increases in metastatic prostate cancer began in the years before its release. Changes in aggregate screening before the USPSTF grade D recommendation, alterations in the biological aggressiveness of prostate cancer or increases in the ascertainment of metastatic disease (through increased sensitivity and utilization of imaging) are plausible explanations. Although the latter is possible, it seems less likely given increased imaging would discover metastases in more men with lower PSAs and we noted the opposite, a simultaneous increase in PSAs among men with metastatic prostate cancer.

Although the social and biologic factors underlying these PSA escapes and rising metastatic prostate cancer cases are unknown, the implications of these recent trends highlight the continued

need for nationwide refinements in prostate cancer screening and treatment to prevent the morbidity and mortality associated with metastatic prostate cancer. This will be particularly critical for population health economics in the United States considering the added cost of care for metastatic prostate cancer<sup>7</sup> and an aging constituency whose population over the age 65 years will double to over a projected 80 million by the year 2050.<sup>8</sup> In addition, our findings and forthcoming changes in the number of elderly individuals should provide impetus to improve treatments for men with metastatic prostate cancer whose cancer-specific survival has not changed significantly in the past two decades.<sup>9</sup>

Data from the NCDB also demonstrated an increase in the incidence of intermediate-risk prostate cancer in the early years of the study period. This likely reflects grade migration because of modifications in the Gleason Grading system in 2005 by the International Society of Urologic Pathology leading to Gleason 6 cancers being upgraded.<sup>10</sup> Declines seen in low-risk prostate cancer incidence following the year 2007 likely reflects changes in aggregate screening after the 2008 USPSTF recommendation against screening for the elderly.<sup>1</sup>

Limitations to the current study include the lack of national annual incidence rates in the NCDB. Thus, our outcome variable was annual incidence of prostate cancer at over 1000 health-care facilities in the United States relative to that of 2004, the initial year of our study period. However, given the large number of patients and health-care facilities analyzed, it is likely that trends in the NCDB reflect national patterns.

#### CONFLICT OF INTEREST

The authors declare no conflict of interest.

#### ACKNOWLEDGEMENTS

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