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ORIGINAL ARTICLE

Is prostate cancer stage migration continuing for black men in the PSA era?

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BACKGROUND: In the United States, disease-specific mortality from prostate cancer (PC) is highest among black men. While the introduction of widespread PSA testing has been associated with a downward stage migration, whether this trend continues in the late PSA era and for black men is unknown. The objective of our study was to evaluate current PC stage migration patterns in the United States by race.

METHODS: The Surveillance, Epidemiology and End Results (SEER) registry was queried to obtain all cases of PC reported between 2000 and 2013. Year of diagnosis was categorized into 2000–2003, 2004–2007, 2008–2010 and 2011–2013. Predictors of distant stage PC at diagnosis were determined using logistic regression adjusted for year of diagnosis, age at diagnosis, SEER region and race.

RESULTS: A total of 791 184 PC cases were identified. The cohort comprised 78.9% ($n = 594\,920$) white and 14.1% ($n = 106\,133$) black men. The stage at diagnosis was 83.3% localized, 12.0% regional and 4.7% distant. Age-adjusted incidence demonstrated a steady decline for black men in all time groups while white men had a stable incidence of distant disease between 2000 and 2013. In univariate analysis, black men in the 2004–2007 (OR 0.86 (0.81–0.93)) and 2008–2010 cohorts (OR 0.85 (0.79–0.91)) were less likely to be diagnosed with metastatic PC as compared with the 2000–2003 baseline cohort. In multivariate analysis, the 2004–2007 black cohort was less likely to be diagnosed with distant PC (OR 0.90 (0.84–0.97)). This trend was not observed in white men who in multivariate analysis had an increased risk of distant PC in the 2004–2007 (OR 1.08 (1.04–1.11)), 2008–2010 (OR 1.22 (1.18–1.27)) and 2011–2013 (OR 1.65 (1.59–1.71)) groups.

CONCLUSIONS: PC downward stage migration continues in black men but not in white men. Discontinuation of PSA-based screening for PC could disproportionately affect black men.

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INTRODUCTION

In the United States, the modern era of prostate cancer (PC) screening and treatment began with the Food and Drug Administration approval of PSA in 1986 for use as a serum marker for monitoring treatment response and recurrence.[1] In 1991, Catalona *et al.*[2] published the results of a landmark trial for the use of PSA as a screening test for the detection of PC in asymptomatic men over the age of 50, leading to Food and Drug Administration approval for the use of the PSA test as a population screening test. During this initial era, PSA testing was widely adopted by patients and physicians alike and the number of PC diagnoses sharply increased with the introduction of a screening test to a previously unscreened population.[3] Since then, numerous studies demonstrated a shift towards a lower stage of disease on surgical radical prostatectomy specimens[4–7] as well as a decrease in the number of patients presenting with metastatic PC.[8–10] Despite these trends in pathological staging and metastatic disease, randomized controlled screening trials in the United States[11] and Europe[12] have reached differing conclusions regarding the impact of PSA screening on mortality. This resulted in the US Preventive Services Task Force (USPSTF) recommending against routine PSA screening in 2012.[13]

Numerous studies[14,15] have noted that African ancestry represents a significant risk for the development of PC. Epidemiological studies have noted that African ancestry was associated with an increased incidence and age-adjusted death rates of PC since the 1950s[16] and autopsy data have shown that African-American men have over a fourfold risk of distant PC starting between the ages of 40 and 49.[17] Clinically, black men have been noted to have twice the risk for presenting with advanced stage PC[18] as well as worse survival outcomes[19] when compared with non-Hispanic white men. Like the trends noted in the general population, prior studies have shown that the use of PSA testing resulted in an increased incidence and a downward stage migration (towards a lower stage of disease) in black men.[20] While some report that the downward stage migration stopped in recent years in the general population,[21] it is not clear if this applies to black men.

The objective of our study was to evaluate PC stage migration patterns in the United States during the PSA era stratified by race to identify if trends observed in the general population are applicable to black men. If stage migration is continuing, we hypothesize that discontinuation of PSA screening may disproportionally affect black men. To address this question, we analyzed a large population-based registry of PC cases from 2000 to 2013 to determine temporal trends in diagnosis with distant PC in white and black men in the United States.

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MATERIALS AND METHODS

Cohort

After the project was deemed exempt by the University of Illinois-Chicago Institutional Review Board, data for this study were retrieved from the Surveillance, Epidemiology, and End Results (SEER) 18 public use database, November 2015 submission, a United States population-based registry. The SEER*Stat software, version 8.2.0 (Information Management Services, Silver Spring, MD, USA) was used in client-server mode to perform all data queries. Cases of PC (SEER disease site 61.9, all histological subtypes, primarily adenocarcinoma ICD-0–3 code 8140) in patients 18 years of age or older reported to the SEER registry between 2000 and 2013 were included. Patients with unknown staging information were excluded. Stage at diagnosis was categorized as localized, regional, distant or unknown using SEER summary stage definitions. Race was self-reported and categorized in SEER as White, Black or Other (Asian/Pacific Islander, American Indian/Alaska Native). PC incidence rates were reported as age-adjusted incidence per 100 000 US population. Median family income ($), percentage of families below the poverty line and percentage of adults not attaining highschool education are reported from the US Census at the zipcode level.

Data analysis

All descriptive data are presented as proportions for categorical variables, or medians with interquartile ranges for continuous variables. When plotting the age-adjusted PC incidence rates by stage at diagnosis and race non-linear trends for black men during the 2000–2013 time period were noted (Figure 1a). Therefore, year of diagnosis was categorized into (2000–2003), (2004–2007), (2008–2010) and (2011–2013) using the initial (2000–2003) cohort as the reference group that was selected *a priori*. Predictors of diagnosis with distant PC were determined using logistic regression adjusted for year of diagnosis (categorical), age at diagnosis (continuous and categorized as < 55 years vs $\geqslant 55$ years), SEER region (categorical) and race (categorical). All results are presented as odds ratios (OR) with 95% confidence intervals (CI). A multivariate analysis was performed adjusting for variables that were statistically significant in the univariate analysis, including age, race, educational attainment, median family household income, year of diagnosis and SEER region. All statistical analyses were performed using R version 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

SEER contained 791 184 cases of PC diagnosed among adult males between 2000 and 2013. PC stage at diagnosis was primarily localized 83.3%, ($n = 628\ 447$), while 12.0% ($n = 90\ 850$) and 4.7% ($n = 35\ 194$) of men presented with regional and distant PC, respectively. The cohort comprised 78.9% ($n = 594\ 920$) white men with 14.1% ($n = 106\ 133$) identifying as black. Patients with unknown stage at diagnosis ($n = 36\ 693$) were excluded for a total analysis cohort of 754 491 men. Table 1a shows complete summary statistics for the analysis sample, stratified by race. Black men presented at a younger age with a median age at diagnosis of 64 (IQR 57–71) as compared with a median age of diagnosis of 67 (IQR 60–74) in white men ($P < 0.01$). A higher proportion of black men presented with distant PC compared with white men (6.0% vs 4.4%, $P < 0.01$). Statistically significant ($P < 0.01$) differences were also observed with racial stratification for zipcode level demographic data, including educational attainment, median family income and percentage of families living below the poverty line. Cohort descriptives stratified by stage of PC at presentation are shown in Table 1b. Patients with distant PC at diagnosis were from areas with significantly lower educational attainment, median family income and percentage of families living below the poverty line ($P < 0.01$) While black men comprised 14.1% of the overall analysis, they were disproportionally represented in men presenting with distant PC, comprising 18.2% of that cohort ($P < 0.01$). Patients presenting with distant PC were older with a median age of 73 (IQR 64–81) than men diagnosed with localized PC who had a median age of 67 (IQR 60–74).

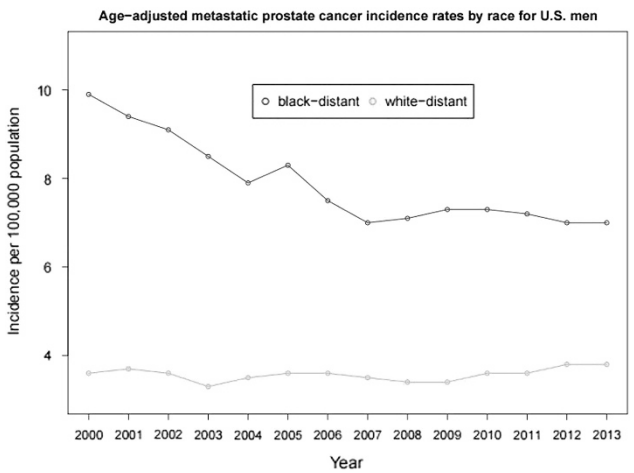

Figure 1a. Age-adjusted metastatic prostate cancer incidence rates by race for US men.

When PC incidence was evaluated as age-adjusted analysis per 100 000 men as shown in Table 2, incidence rates of localized disease demonstrated a steady decrease for all time cohorts for black, white and other men. While localized disease decreased between 2000 to 2013, black men were noted to have a steady decrease in distant presentation from 9.2/100 000 to 7.1/100 000 while conversely white men had a stable trend during this time period from 3.6/100 000 to 3.7/100 000. These trends are shown in Figure 1a. When analyzed as a proportion of PC diagnoses, distant rates decreased steadily for black men between 2000 and 2007 before rising each year until 2013 as shown in Figure 1b. Conversely, white men demonstrated a stable proportion of distant PC diagnoses between 2000 and 2007 before demonstrating a similar rise to black men between 2007 and 2013.

Odds ratios for univariate predictors of metastatic PC at the time of diagnosis, including age, year of diagnosis, black race, median family income and educational attainment are shown in Table 3. Black race (OR 1.38 (1.34–1.42), $P < 0.01$) was a risk factor for distant diagnosis while when age was categorized; diagnosis < 55 years of age was associated with a reduced likelihood of distant stage (OR 0.63 (0.60–0.66), $P < 0.01$). On univariate analysis, black men in the 2004–2007 (OR 0.86 (0.81–0.93), $P < 0.01$) and 2008–2010 cohorts (OR 0.85 (0.79–0.91), $P < 0.01$) were significantly less likely to be diagnosed with metastatic PC as compared with the 2000–2003 baseline cohort while the 2011–2013 cohort (OR 1.01 (0.94–1.09), $P = 0.73$) did not demonstrate a significant change in risk. Conversely, white men in the 2004–2007 (OR 1.03 (1.00–1.07), $P = 0.05$), the 2008–2010 cohort (OR 1.08 (1.04–1.12), $P < 0.01$) and 2011–2013 cohort (OR 1.44 (1.39–1.49), $P < 0.01$) were significantly more likely to be diagnosed with distant PC.

On multivariate analysis shown in Table 4, which adjusted for age, race, educational attainment, household income, year of diagnosis and SEER region, the 2004–2007 black cohort was significantly less likely to be diagnosed with distant PC (OR 0.90 (0.84–0.97), $P < 0.01$); however, the 2008–2010 black cohort (OR 0.94 (0.87–1.01), $P = 0.09$) was not significantly different and the 2011–2013 black cohort (OR 1.13 (1.05–1.22), $P < 0.01$) was significantly more likely to present with distant disease as compared with the baseline cohort. However, for white men there was a statistically significant trend with increased rates of metastatic presentations in the 2004–2007 (OR = 1.08 (1.04–1.11), $P < 0.01$), 2008–2010 (OR = 1.22 (1.18–1.27), $P < 0.01$) and 2011–2013 (OR 1.65 (1.59–1.71), $P < 0.01$) cohorts.

Table 1a. Cohort descriptives stratified by race

	Race				*P*
	White	*Black*	*Other*	*Unknown*	
N	594 920 (78.85%)	106 133 (14.07%)	36 071 (4.78%)	17 367 (2.30%)	
Stage at diagnosis					< 0.01
Distant	26 400 (4.44%)	6 396 (6.03%)	2 112 (5.86%)	286 (1.65%)	
Localized	494 427 (83.11%)	88 344 (83.24%)	29 281 (81.18%)	16 395 (94.40%)	
Regionalized	74 093 (12.45%)	11 393 (10.73%)	4 678 (12.97%)	686 (3.95%)	
Age at diagnosis (median years and IQR)	67 (60–74)	64 (57–71)	69 (62–75)	68 (60–76)	< 0.01
Median year of diagnosis (continuous)	2006 (2003–2010)	2007 (2003–2010)	2007 (2003–2010)	2008 (2005–2011)	< 0.01
Median educational attainment (% without completing high school)	13.50 (10.29–18.92)	16.07 (11.93–20.05)	13.79 (9.63–20.76)	16.18 (11.93–23.24)	< 0.01
Median % families below poverty level (IQR)	9.42 (7.15–13.65)	13.28 (9.07–17.17)	8.3 (6.74–13.65)	9.98 (7.99–13.67)	< 0.01
$ median family income (IQR)	$68 630 (60 690–84 190)	$62 630 (52 680–76 600)	$84 640 (62 630–88 170)	$69 300 (62 630–85 140)	< 0.01

All descriptive data are presented as proportions for categorical variables, or medians with interquartile ranges (IQRs) for continuous variables.

DISCUSSION

This study aimed to determine whether downward PC stage migration was continuing in US men, and whether it differed by race. Using a nationally representative registry, we found that during 2000 to 2013 there exists a difference in stage migration trends between white and black men. Our data suggest that the rate of distant PC at diagnosis continues to decrease in black men, but is increasing in white men. When the analyses were adjusted for available demographic and socioeconomic covariates, the results remained similar.

Since the introduction of PSA testing in 1986, the rates of distant PC at the time of presentation in the overall US population have decreased by half.[22] Scosyrev *et al*.[8] compared the rates of metastatic PC between 1988 (prior to PSA screening) and 2008 and found a threefold reduction in the incidence, which was consistent when stratified by race. These trends did vary by age, with the largest downward stage migration occurring in men over 70. In a previous SEER study, Powell *et al*.[23] found that while African-American men had significantly shorter survival between 1973–1994, they had similar survival between 1995 to 2005 for stage-matched PC; however, like our study, the burden of metastatic disease was still higher for African-American men. In our study, which was adjusted for age at diagnosis and included more updated time periods, we found a divergence in the trends for white men, with a stabilization and possible reversal to an upward stage migration. Concern for an upward PC stage migration was expressed in a recently published cohort study using the National Cancer Data Base which demonstrated an increasing incidence of metastatic PC between 2007 and 2013.[24] While this study did find the largest increase in metastatic PC incidence in men between ages 55–69, it did not assess for racial differences in these trends.

While the mechanisms underlying our observations cannot be proven by these data, we propose several hypotheses for the trends we observe. While the rates of PSA testing have declined overall in the United States on the heels of the USPSTF recommendations,[25] most advocate that high-risk populations such as black men may benefit from screening. As such, the downward stage migration could represent increasingly rigorous PSA screening in black men relative to white men during the study period. During the initial introduction of PSA testing, it was noted that PC screening events such as those held during Prostate Cancer Awareness Week attracted a disproportionate number of white men compared with the more diverse catchment areas these events drew from.[26] Similarly, black men during this time period were found to be significantly less likely to have ever had a digital rectal examination or have PSA testing performed.[27] This is in contrast with the most recent data from the National Health Insurance Survey which showed similar rates of PSA screening utilization in white and black men.[28]

Several screening guidelines recommend earlier initiation of PSA screening for black men.[29–32] While we cannot directly attribute our results to changes in screening, an increase in metastatic presentation in white men due to decreased screening would be consistent with studies that demonstrated decreased rates of PSA screening for all men prior to USPSTF recommendation changes as well as with the results of the ERSPC screening trial which found a reduction in metastases by 30% in the screening arm.[33]

While our study period mostly precludes the 2012 USPSTF downgrade of PSA testing to 'D' (not recommended), there had already been concern with overdetection and overtreatment of indolent PC in the US evidenced in part by the increased adoption to active surveillance.[34] While screening utilization cannot be ascertained in the SEER data, it is possible that PSA testing has differentially decreased in white men. Indeed, this trend was evident in an analysis of the National Health Interview Survey but did not reach statistical significance.[25] Another possible explanation for our findings is that black men are getting earlier referral for biopsy, given increasing awareness of the race disparity in PC death. This was not evident in the PLCO (Prostate, Lung, Colorectal and Ovarian) Cancer Screening Trial;[35] however, it was shown black men were less likely than white men to get follow-up and subsequent prostate biopsy for an elevated PSA.[36] A confounder to stage at diagnosis could be detection bias related to advances in imaging. It has been proposed by several groups that anteriorly located prostate tumors are delayed in diagnosis and more commonly occur in black men.[37,38] Theoretically the increasing use of 3 T magnetic resonance imaging could be therefore differentially improving detection in black men. In addition, more sensitive imaging modalities for metastases such as NaF positron emission tomography scans and whole-body diffused weighted magnetic resonance imaging may cause a stage migration to metastatic in men who have previously been thought to have

Table 1b. Cohort descriptives stratified by stage at diagnosis

	PC stage at diagnosis			*P*
	Localized	*Regional*	*Distant*	
N	628 447 (83.29%)	90 850 (12.04%)	35 194 (4.66%)	
Race				< 0.01
White	494 427 (78.67%)	74 093 (81.56%)	26 400 (75.01%)	
Black	88 344 (14.06%)	11 393 (12.54%)	6 396 (18.17%)	
Other	29 281 (4.66%)	4 678 (5.15%)	2 112 (6.00%)	
Unknown	16 395 (2.61%)	686 (0.76%)	286 (0.81%)	
Median age at diagnosis (years & IQR)	67 (60–74)	63 (58–68)	73 (64–81)	< 0.01
Median year of diagnosis (IQR)	2007 (2003–2010)	2007 (2003–2010)	2007 (2003–2010)	< 0.01
Median educational attainment (% without completing high school)	13.79% (10.50–18.99)	14.09% (10.50–20.35)	14.43% (10.99–20.76)	< 0.01
Median % families below poverty line	9.98 (7.15–13.67)	9.75 (7.43–13.67)	9.98 (7.44–13.67)	< 0.01
Median family income (IQR)	$68 410 (60 200–84 190)	$67 500 (60 710–84 190)	$66 510 (60 170–84 190)	< 0.01

Abbreviations: IQR, interquartile range; PC, prostate cancer.

Table 2. Age-adjusted prostate cancer incidence rates (per 100 000) during 2000–2013 study interval

Stage	*Year of diagnosis*	*Black*	*White*	*Other*
Localized	2000–2003	109.0	75.2	44.0
Localized	2004–2007	105.2	71.8	39.9
Localized	2008–2010	99.6	65.4	32.6
Localized	2011–2013	81.3	51.5	25.0
Regional	2000–2003	14.3	10.6	5.4
Regional	2004–2007	11.4	9.8	5.4
Regional	2008–2010	11.2	9.7	5.2
Regional	2011–2013	9.5	8.2	4.6
Distant	2000–2003	9.2	3.6	3.0
Distant	2004–2007	7.7	3.5	2.8
Distant	2008–2010	7.2	3.5	2.6
Distant	2011–2013	7.1	3.7	2.4

Table 3. Predictors of distant stage PC at time of diagnosis (univariate)

Parameters	*OR*	*95% CI*	P
Age < 55 years	0.63	0.60–0.66	< 0.01
Year of diagnosis			
2000–2003 (ref.)			
2004–2007	1.00	0.97–1.03	0.83
2008–2010	1.04	1.01–1.07	0.03
2011–2013	1.33	1.29-1.37	< 0.01
Race			
Non-black (ref.)			
Black	1.38	1.34–1.42	< 0.01
Median family income (below cohort median)	1.09	1.07–1.11	< 0.01
% not attaining high school	1.01	1.01–1.01	< 0.01

Abbreviations: CI, confidence interval; OR, odds ratio; PC, prostate cancer.

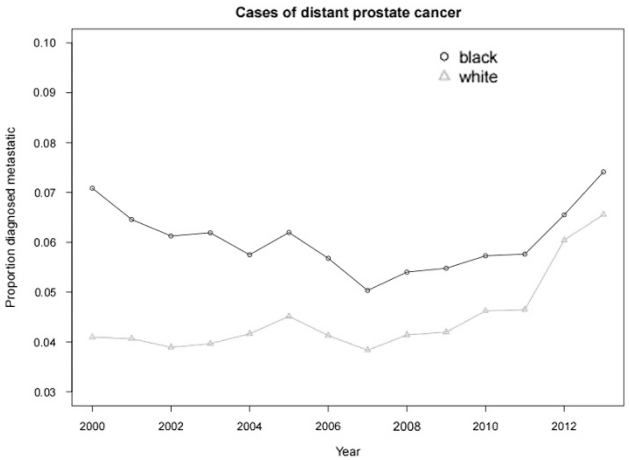

Figure 1b. Cases of distant prostate cancer.

localized tumors.[39,40] If there was less access to these technologies for black men compared with white men, for example, it could simultaneously reduce the stage at diagnosis for black men while increasing it in white men.

Like previous population studies, our study confirms that black men continue to have significantly higher rates of both localized and distant PC as compared with whites and that older men have a higher risk of developing metastatic PC. The mechanisms for this race disparity are likely due to multiple factors that are socioeconomic, genetic or treatment related.[41–47]

As national registry data continue to mature after 2012, it will be important to continue to monitor the trends of distant disease at presentation. While ultimately changes in mortality will be important to monitor, we will expect a long lead time for these changes to be affected by screening policy. Stage at diagnosis serves as a surrogate outcome measure for survival as PC represents a significant proportion of mortalities in men with metastatic disease.[48] With regard to race disparities, using stage at diagnosis removes major possible confounding variables such as treatment choice and adherence.

There are several limitations to our study that are important to consider. Since SEER only includes data through 2013, we only have the initial period of time following the 2012 USPSTF recommendations on PSA screening and our data may not fully capture if changes have occurred to stage at diagnosis since this policy shift may not reflect current presentation patterns. Additionally, inherent to use with the SEER database, our study

Table 4. Odds ratios for distant presentation (multivariate)

	Adjusted odds of distant PC at diagnosis								
	2004–2007			*2008–2010*			*2011–2013*		
	OR	*95% CI*	P-*value*	*OR*	*95% CI*	P-*value*	*OR*	*95% CI*	P-*value*
Black	0.90	0.84–0.97	< 0.01	0.94	0.87–1.01	0.09	1.13	1.05–1.22	< 0.01
White	1.08	1.04–1.11	< 0.01	1.22	1.18–1.27	< 0.01	1.65	1.59–1.71	< 0.01
All[a]	1.04	1.01–1.07	< 0.01	1.17	1.13–1.20	< 0.01	1.53	1.48–1.57	< 0.01
Other	1.06	0.94–1.20	0.33	1.28	1.12–1.45	< 0.01	1.51	1.33–1.72	< 0.01

Abbreviations: CI, confidence interval; OR, odds ratio; PC, prostate cancer. Adjusted for age at diagnosis, region, family income, educational attainment (data not shown) (referent to 2000–2003). [a]Also adjusted for race.

does not have screening data and thus information regarding the initiation and frequency of PC screening practices, which may vary between white and black men and could contribute towards differences in outcomes, is speculative in nature. Another potential limitation is that the SEER registry codes both white and Hispanic/Latino men together in one category as white men, while these groups do have relatively comparable incidence and mortality data[49] there may be some bias introduced by this classification, although we feel it is minimal. Finally, our data set utilizes self-reported race which has been previously shown to have significant variance from genetic ancestry obtained from ancestry informative markers.[50] Thus, self-reported race may not appropriately provide an accurate risk assessment for the development of metastatic PC. Despite these limitations, we believe our study is the first to examine racial differences in PC stage migration using a large population-based sample using both incidence and case level data to analyze trends for PC stage of diagnosis. This study is also valuable because it helps to clarify that while the proportion of distant diagnoses for both white and black men has risen in recent years, the age-adjusted incidence of disease has been decreasing for black men but stable for white men.

CONCLUSIONS

In the contemporary PSA era PC stage migration towards a lower stage of disease is still occurring among black men but appears to have stabilized among white men. Discontinuation of PSA-based screening for PC could disproportionately affect black men, who, as a group, remain most likely to be diagnosed with metastatic and potentially fatal disease.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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