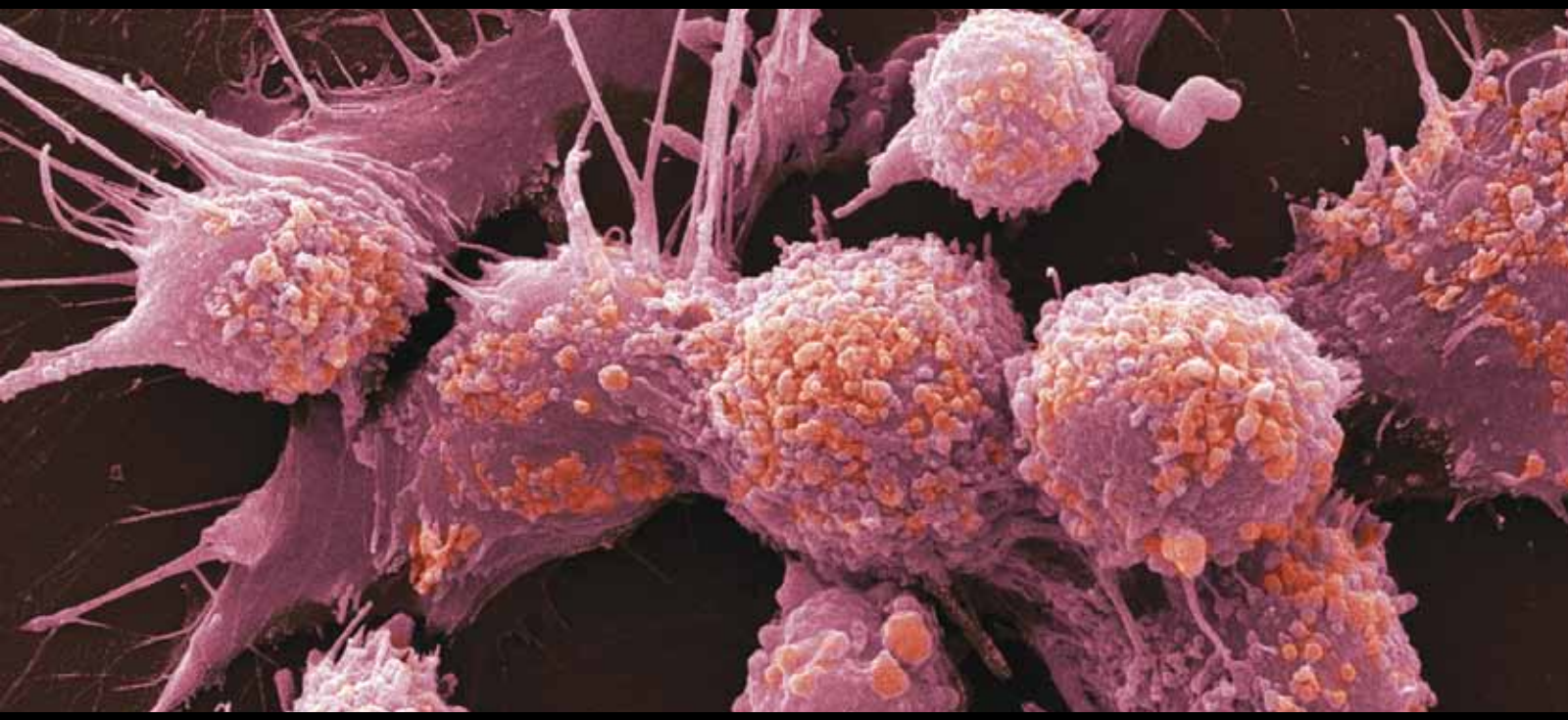
Racial Disparities in Prostate Cancer Incidence, Biochemical Recurrence, and Mortality

Guest Editors: Cathryn Bock, Rick Kittles, Isaac Powell, John Carpten, and Ann Hsing



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Editorial

Racial Disparities in Prostate Cancer Incidence, Biochemical Recurrence, and Mortality

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Prostate cancer incidence and mortality rates vary widely among populations, with the highest documented rates among American and Caribbean men of African descent and the lowest rates in Asian populations. It is likely that these differences can be attributed to variation in genetics, environmental exposures, access to health care, screening patterns, and treatment patterns; however, the reasons for these differences have not been fully elucidated.

This special issue includes eight original research articles that provide details regarding racial differences in incidence rates and mortality rates and pathological features and which help us to achieve a better understanding of environmental and clinical reasons for these disparities. Two of the articles examine the validity of prognostic indicators and treatment recommendations in populations external to those in which nomograms and treatment protocols were developed.

The first research article, "*Prostate cancer incidence rates in Africa,*" characterizes incidence rates within Sub-Saharan Africa populations. Despite differences in data availability and quality across the various locations included, the authors provide strong evidence that incidence rates vary considerably within Africa and that incidence rates are rising in several Sub-Saharan Africa countries. The reported incidence rates in Africa are much lower than those among African American men but are similar to incidence rates of *distant-stage* prostate cancer in African American men.

The next two articles address issues in prostate cancer rates in Caribbean nations. A. J. M. Hennis et al. describe prostate cancer incidence and mortality rates in Barbados and compare these with rates among several other populations in "*Prostate cancer incidence and mortality in Barbados, West Indies*." In general, rates in Barbados do not differ from rates in other Carribbean populations and are lower than those reported in African Americans. In "*Environment as a potential key determinant of the continued increase of prostate cancer incidence in Martinique*," D. Belpomme and P. Irigaray identified higher prostate cancer incidence rates in Martinique compared with those in France, Sweden, the USA, and the UK. Reasons for incidence rate differences were examined using an ecological study approach, and evidence favored genetic, pesticide exposure, or gene-environment interaction explanations for rate differences, with no evidence observed for a role of life expectancy or diet on differences in incidence rates.

Important pathological differences in disease characteristics by race are described in the fourth paper, "*A retrospective study on pathologic features and racial disparities in prostate cancer*." S. A. Bigler et al. report differences in the prevalence of key histologic and clinical features between African American and Caucasian men at times of biopsy, diagnosis, and prostatectomy. These differences include younger age, higher cancer detection rate, higher Gleason score, more bilateral prostate involvement, larger prostate size, and greater tumor volume among African American men compared with Caucasian men. Differences in tumor evolution described include increased risk of diagnosis of

prostate cancer associated with diagnosis of high-grade prostatic intraepithelial neoplasia (HGPIN) or atypical small acinar proliferation (ASAP) among African American men and shorter time from noncancerous biopsy to diagnostic biopsy among men with HGPIN, with ASAP, or of African American race.

In the fifth article, "*The metabolic syndrome and biochemical recurrence following radical prostatectomy*" by J. M. Post et al., hypertension was the most common metabolic feature in both African American and Caucasian prostate cancer cases, with a significantly greater presence among African American men with prostate cancer. Metabolic syndrome was associated with a 50% increase in risk of biochemical recurrence (BCR), and hypertension was associated with a two-fold increase in risk of BCR among both African Americans and Caucasians.

In the sixth article, "*Prostate cancer severity associations with neighborhood deprivation*," C. M. Ziegler-Johnson et al. report associations between several measures of neighborhood and increased prostate cancer severity in neighborhoods in Southeastern Pennsylvania, with the greatest evidence for association observed within African Americans.

In the seventh article, "*Racial/ethnic patterns in prostate cancer outcomes in an active surveillance cohort,*" J. Cullen et al. compare secondary treatment and overall survival by race/ethnicity in a cohort of men followed on an active surveillance protocol. While black patients were more likely to undergo secondary treatment, no racial differences in overall survival were detected. Given current concerns in the field regarding the overtreatment of prostate cancer and whether active surveillance is appropriate in black men, these findings provide reassuring evidence that, at least when secondary treatment availability is equal, there are no differences in overall survival by race.

In the eighth article, "*Development and external validation of a nomogram predicting the probability of significant Gleason sum upgrading among Japanese patients with localized prostate cancer*," T. Imamoto et al. describe a nomogram for predicting Gleason sum upgrading from biopsy to radical prostatectomy with better validity in Japanese men than a previous nomogram developed in a Western population. Given that approximately one-fifth of Japanese men diagnosed with prostate cancer at biopsy will experience Gleason sum upgrade, this nomogram may aid clinicians in identifying patients at higher risk of upgrade.

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Research Article

Prostate Cancer Incidence Rates in Africa

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African American men have among the highest prostate cancer incidence rates in the world yet rates among their African counterparts are unclear. In this paper, we compared reported rates among black men of Sub-Saharan African descent using data from the International Agency for Research on Cancer (IARC) and the National Cancer Institute Surveillance, Epidemiology, and End Results Program for 1973–2007. Although population-based data in Africa are quite limited, the available data from IARC showed that rates among blacks were highest in the East (10.7–38.1 per 100,000 man-years, age-adjusted world standard) and lowest in the West (4.7–19.8). These rates were considerably lower than those of 80.0–195.3 observed among African Americans. Rates in Africa increased over time (1987–2002) and have been comparable to those for distant stage in African Americans. These patterns are likely due to differences between African and African American men in medical care access, screening, registry quality, genetic diversity, and Westernization. Incidence rates in Africa will likely continue to rise with improving economies and increasing Westernization, warranting the need for more high-quality population-based registration to monitor cancer incidence in Africa.

1. Introduction

African American men have among the highest reported prostate cancer rates in the world [1, 2]. However, whether similarly high rates occur among men in Africa is unclear [3]. Previous reports from Africa were mostly limited to case series and hospital-based data, largely due to the difficulty in establishing high-quality population-based cancer registries in Africa [3–6]. Because West Africans and African Americans share a common genetic ancestry yet have very different lifestyles, a better understanding of prostate cancer rates and patterns among Sub-Saharan Africans may provide unique insights into the etiology of this disease [7]. Therefore, we examined available 1973–2007 incidence rates from Sub-Saharan Africa and the United States (US).

2. Materials and Methods

We used prostate cancer incidence data for Africa from publications of the International Agency for Research on Cancer (IARC; http://www-dep.iarc.fr/): (1) Cancer Incidence in Five Continents (CI5), volumes IV-IX [4, 8] and (2) Cancer in Africa: Epidemiology and Prevention [3]. We included only registries that reported at least 10 cases of prostate cancer that were diagnosed during each time period and from countries that had populations that were more than 95% Black African or reported rates specific to Blacks. Twelve African registries fit these criteria (see Table 1); none of the registries in North or Central Africa met the inclusion criteria. Of the 12 registries selected, nine registries are population based with data collected at the national (The Gambia and Swaziland) or regional (Conakry, Guinea; Bamako, Mali; Niamey, Niger; Ibadan, Nigeria; Eldoret, Kenya; Blantyre, Malawi; Kyadondo, Uganda; Harare, Zimbabwe: African) levels. Of the other three registries, Blantyre, Malawi did not have cancer information based on death certificates due to absence of death registration in the country, South Africa is primarily pathology-based, and Namibia is primarily pathology based with some cases registered from the oncology services in its capital and largest city of Windhoek; it was not

reported whether South Africa or Namibia included cancer information from death certificates.

For comparison with these African data, we calculated rates for US Blacks and Whites from the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) Program for the original nine registries combined using SEER*Stat version 7.0.4 (http://www.seer.cancer.gov/seerstat; NCI, Bethesda, Md) for total prostate cancer [10]. Although SEER expanded to include 13 registries in 1992 and further to 17 registries in 2000, to maintain geographic homogeneity over time, we restricted our analysis to the original 9 registries throughout. SEER annually provides updated rates, which for the earlier years are very similar to those reported in CI5 (data not shown). SEER includes stage-specific data, which are not reported in CI5. Classification of the prostate cancer stage at diagnosis has not been consistent over the 35-year period of the SEER program, with difficulties becoming apparent in delineating localized versus regional stage and more recently localized versus unknown stage. It appeared, however, that the definition and determination of distant-stage disease was more consistent over time, so we calculated rates according to SEER historical stage distant versus nondistant, including localized/regional and stage unknown [10]. The SEER November 2004 submission data file was used to calculate the stage-specific rates for cases diagnosed during 1973–1987 [11] and the November 2009 data file for cases diagnosed during 1988–2007 [10]. Cases that are distant stage at diagnosis in the US are likely to be clinically apparent and perhaps more comparable to most cases diagnosed in Africa. All rates were directly age adjusted to Segi's world standard population [9] and expressed per 100,000 man-years. 95% confidence intervals (CI) extracted from CI5, were estimated for data from Cancer in Africa (see table footnote for method), or provided by SEER*Stat.

We examined trends for SEER during 1973–2007 and for three African registries that reported rates for at least three time points during that time period. We used log scales to plot the rates such that a slope of 10 degrees portrayed a change of 1% per year (Origin version 8.0; OriginLab Corporation, Northampton, Ma, USA) [12].

3. Results and Discussion

Among the African countries, the number of cases ranged from 20 in The Gambia (1997-1998) to 3,432 in South African Blacks (1989–1992) (Table 1). Incidence varied substantially by region, with rates highest in the East (10.7–38.1 per 100,000 man-years), intermediate in the South (14.3–21.8), and lowest in the West (4.7–19.8). The reported rate for Harare, Zimbabwe (38.1 during 1998–2002) was 8 times the rate in The Gambia (4.7 during 1997-1998). In comparison, rates among US Blacks were considerably higher up to 40 times those in Africa: 195.3 in US Blacks during 1993–1997 versus 4.7 in The Gambia during 1997-1998.

Reasons for the large variation of prostate cancer in blacks within the African continent and the observed East-West disparity are unclear but are likely related to differences in medical care access, registry quality, including completeness of case ascertainment and estimates of populations at risk, screening practices, as well as lifestyle factors in subpopulations [4]. For most of Africa, medical care access is limited, with only 4% of Ghanaian men in 2004–2006, for instance, having health insurance (unpublished data); in contrast, about 80% of non-Hispanic blacks in the U.S. had some type of health insurance coverage in 2008 [13]. In the more developed country of South Africa, diagnostic and screening facilities may be more accessible to the general population, but the racial disparity seen in prostate cancer incidence between blacks and whites [7] suggest that blacks may still have poorer access to medical care. Postapartheid, access to medical aid for whites were about seven times that of blacks [14]. Underdiagnosis of prostate cancer is likely in populations with limited health care access [3, 7].

Quality of the medical care systems and registries also may have a substantial impact on the completeness and accuracy of the reported incidence rates. Availability of pathology services (reflected by percent of cases microscopically verified; Table 1) likely compromises the quality of cancer diagnosis. For example, in The Gambia, which had the lowest prostate cancer incidence rate, only 20% of cases were morphologically verified during 1997-1998 [4]. In contrast, in Harare, Zimbabwe, which had the highest incidence rate, 63% of cases had morphological verification during 1998–2002 [8]. Both countries had much lower pathological confirmation rates of cancer than the US, where more than 93% of cases have been histologically confirmed since 1973 [10]. On the other hand, a high confirmation rate, such as in Namibia (97%) and South African Blacks (100%), suggests that the registry relied primarily on pathology records and that nonconfirmed cases were not included. A high proportion of cases that were ascertained based on death certificates only suggests that case finding has failed to identify cases that have not died, again potentially resulting in rate underestimation. This may occur in populations with limited infrastructure to support comprehensive data collection [3, 15], especially when diseases like cancer are less of a priority [16, 17]. Thus, the true prostate cancer incidence in African men is likely higher than what is reported here. There also may be uncertainties in the accuracy of the population enumerations and estimates of person-years at risk [4, 8], which could result in either under- or overestimation of the rates.

Unlike the US where increasing and widespread use of prostate-specific antigen (PSA) screening contributed to the rapid rise in incidence during the early 1990s [18], the rising Sub-Saharan African rates were similar to the increases seen for total rates in the US before PSA screening was implemented (Figure 1). PSA screening is still uncommon in most parts of Sub-Saharan Africa, with reported prevalence of 2.5% in Ghana (unpublished data) and 4% in Senegal [19]. Within the SEER data, rates were consistently higher among blacks than whites, rose through the 1990s, especially rapidly during 1980s–1990s overall and for nondistant disease stage before leveling off during the 2000s, and declined notably for distant stage since 1990. Notably, while the total prostate cancer rates in the US were consistently much higher than those in Africa, total rates in East Africa

Table 1: Age-adjusted prostate cancer incidence rates[a] per 100,000 man-years, 95% confidence intervals (CIs), percent microscopically verified, and percent reported by death certificate only in Sub-Saharan Africa and the United States, 1973–2007.

Location and/or race	Source	Time period	No. cases	Incidence rate[a]	95% CI[b]	Microscopically verified (%)	Death certificate only (%)
East Africa							
Blantyre, Malawi	Cancer in Africa	2000-2001	30	10.7	6.9–14.5	47	NK
Eldoret, Kenya	Cancer in Africa	1998–2000	54	16.8	12.3–21.3	30	NK
Harare, Zimbabwe: African	CI5 VII	1990–1992	112	28.3	22.5–43.1	64	9
	CI5 VIII	1993–1997	251	30.7	26.5–34.9	56	15
	CI5 IX	1998–2002	418	38.1	34.1–42.1	63	15
Kyadondo, Uganda	CI5 VII	1991–1993	86	27.7	21.6–33.8	67	NK
	CI5 VIII	1993–1997	215	37.1	31.7–42.5	77	0
	CI5 IX	1998–2002	262	37.6	32.8–42.4	58	NK
Southern Africa							
Namibia	Cancer in Africa	1995–1998	352	21.8	19.5–24.1	97	NK
South Africa: blacks	Cancer in Africa	1989–1992	3432	14.3	13.8–14.8	100	NK
Swaziland	Cancer in Africa	1996–1999	153	21.5	18.1–24.9	24	NK
West Africa							
Bamako, Mali	CI5 VI	1987–1989	21	6.3	3.5–9.1	5	5
	CI5 VII	1988–1992	33	5.2	3.4–7.0	21	6
	CI5 VIII	1994–1996	29	7.6	4.8–10.4	55	3
Conakry, Guinea	Cancer in Africa	1996–1999	62	9.7	7.3–12.1	45	NK
Ibadan, Nigeria	Cancer in Africa	1998–1999	115	19.8	16.2–23.4	70	NK
Niamey, Niger	Cancer in Africa	1993–1999	41	10.8	7.5–14.1	34	NK
The Gambia	CI5 VIII	1997-1998	20	4.7	2.5–6.9	20	NK
North America							
United States							
Blacks	NCI-SEER	1973–1977	2666	80	77.0–83.1	93	1
	NCI-SEER	1978–1982	3783	89.8	86.8–92.6	95	1
	NCI-SEER	1983–1987	4754	100.0	97.1–102.8	96	1
	NCI-SEER	1988–1992	7511	143.3	140.1–146.6	97	0
	NCI-SEER	1993–1997	10853	195.9	191.6–199.1	96	1
	NCI-SEER	1998–2002	11940	192.9	186.6–193.7	97	1
	NCI-SEER	2003–2007	12618	172.8	169.8–176.0	98	1
Whites	NCI-SEER	1973–1977	24212	47.9	47.3–48.5	94	1
	NCI-SEER	1978–1982	31389	54.8	54.1–55.3	95	1
	NCI-SEER	1983–1987	39492	63.5	62.8–64.0	97	0
	NCI-SEER	1988–1992	68863	104.3	103.3–104.9	96	1
	NCI-SEER	1993–1997	73687	111.8	110.5–112.2	97	1
	NCI-SEER	1998–2002	80100	116.9	115.1–116.8	97	1
	NCI-SEER	2003–2007	80022	107.0	106.2–107.8	98	1

CI: confidence interval; NK: not known; CI5: Cancer Incidence in Five Continents; NCI-SEER: National Cancer Institute's Surveillance, Epidemiology, and End Results Program: nine registries.

[a]All rates are age adjusted to Segi's world standard population [9]; African rates are shown only for populations at least 95% black or are specific for black Africans.

[b]95% CIs were obtained directly from CI5, were estimated for data from the Cancer in Africa publication by multiplying the standard error (incidence rate divided by the square root of the total number of cases) by 1.96, and adding to and subtracting from the incidence rate to obtain the upper and lower bounds, respectively, or were provided by SEER*Stat.

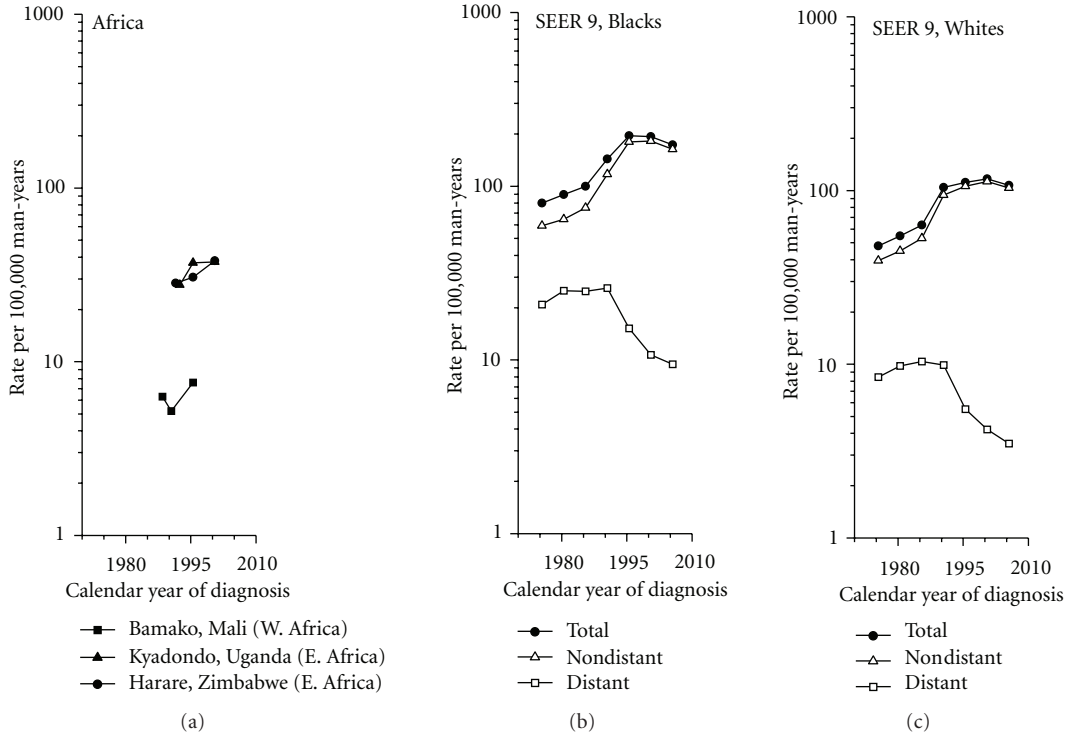

Figure 1: Age-adjusted (Segi's world standard) prostate cancer incidence in Sub-Saharan Africa and the United States, 1973–2007. (a) Africa: total prostate cancer rates from registries in three African cities; the populations of both Mali and Uganda were >95% black, and the rates for Zimbabwe were specific for black Africans. US: SEER nine registries combined for blacks (b) and whites (c): total and by SEER historical stage: nondistant and distant. All rates are for 3–5 year time periods (see Table 1).

(Uganda and Zimbabwe) were similar to the distant-stage rate among black Americans during the 1980s. Total rates in East Africa have also been higher than distant-stage rates reported for black and white Americans in recent years. This observation is also consistent with the fact that screening is uncommon in Africa, and thus cancers are more likely diagnosed at a more advanced stage. In fact, advanced disease accounted for 75% of cases in Ghana (unpublished data) and 47.9% in Senegal [20].

Similar to reasons given above for the geographic variation in rates within Africa, it is likely that improved health care systems and better ascertainment and reporting of cases may contribute to the rising rates in Africa [7, 21]. However, it is also possible that increased westernization in Africa in recent years, including changes in diet and lifestyle, may also play a role. For example, recent population-based data from Ghana show that the prevalence of obesity, a potential effect of Westernization, increased from 5% in 1998 [22] to 9% in 2004–2006, and the prevalence of overweight increased from 17% to 32% (unpublished data). US non-Hispanic Black men had a prevalence of obesity and overweight of 34.0% and 69.1%, respectively, in 2003-2004 [23]. Both clinical and etiologic investigations in African men are needed to further clarify reasons for the rising prostate cancer incidence in Africa.

Considering that the level of Westernization in Africa is still much lower than that in the US, the observation that total incidence rates in East Africa (Zimbabwe and Uganda), even in the earlier time period, were slightly higher than those of distant stage disease among African Americans is consistent with recent findings from genome-wide association studies (GWAS) showing that genetics are an important factor in prostate cancer. Recent GWAS have linked over 30 independent genetic loci to higher risks of prostate cancer in populations of European descent, including multiple loci in chromosome 8q24 [24–35]. Notably, some of the known risk alleles in 8q24 are more common in African Americans than non-African populations [28], suggesting that genetic variation may contribute to racial disparities between African American and other populations. In a large study of GWAS-identified risk variants and prostate cancer in African Americans, significant associations were found for some of the GWAS-identified risk variants in the same direction and of similar magnitude as those reported in men of European descent [36]. Most notably, all reported risk loci at 8q24 were significantly associated with prostate cancer with 8q24 region 2 attaining genome-wide significance levels. A recent GWAS specific to men of African descent also found similar results for previously identified variants in 8q24 but discovered an additional susceptibility locus at 17q21 [37]. It is noteworthy that the frequency of the 17q21 risk variation (rs7210100) is 4 to 7% in men of African ancestry, including Ghanaian men (7%), but is less than 1% in non-African populations (based on data from the 1000 Genomes Project). This novel finding suggests that some risk loci may be specific to African populations. Whether 8q24, 17q21, or other risk variants

play an important role in prostate cancer in African men warrants further confirmation, and future studies are needed to determine their underlying biological mechanisms.

In a previous publication, Parkin et al. [7] found that the highest estimated rates of prostate cancer in Africa were seen in the South followed by Central, West, East, and North African regions. However, these 2008 estimates were for regional populations of all races combined and thus are not necessarily specific to blacks. For example, Parkin et al. [7] noted that the high rate of 40.5 per 100,000 man-years reported for Southern Africa was the composite of the rates among various racial groups. In South Africa alone, the rates ranged from a high of 41.1 per 100,000 man-years among whites, to 25.4 among mixed races, 14.3 among blacks, and 13.0 among Indians [3]. Because race is a well-established risk factor for prostate cancer, a more comparable assessment of prostate cancer rates in Africa for comparison with African Americans necessitates comparison of black-specific rates, as in the current study.

4. Conclusions

Although data are limited, our analysis showed that (1) reported total prostate cancer incidence in Africa is lower than that among African Americans; (2) rates vary substantially (8-fold) within Sub-Saharan Africa, with rates lowest in the West and highest in the East; (3) total prostate cancer rates in Africa are similar to distant-stage disease rates in the US; (4) incidence appears to be rising in several African countries. It should be noted that when making inferences from these findings, consideration should be given to limitations in data quality. Undoubtedly, with improved economies and clinical diagnosis as well as increased Westernization, incidence rates in Africa are likely to continue to rise. Therefore, a high priority in this population should be the implementation of high-quality population-based cancer registration to monitor incidence rates in Africa and to develop effective cancer prevention strategies.

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Research Article

Prostate Cancer Incidence and Mortality in Barbados, West Indies

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We describe prostate cancer incidence and mortality in Barbados, West Indies. We ascertained all histologically confirmed cases of prostate cancer during the period July 2002 to December 2008 and reviewed each death registration citing prostate cancer over a 14-year period commencing January 1995. There were 1101 new cases for an incidence rate of 160.4 (95% Confidence Interval: 151.0–170.2) per 100,000 standardized to the US population. Comparable rates in African-American and White American men were 248.2 (95% CI: 246.0–250.5) and 158.0 (95% CI: 157.5–158.6) per 100,000, respectively. Prostate cancer mortality rates in Barbados ranged from 63.2 to 101.6 per 100,000, compared to 51.1 to 78.8 per 100,000 among African Americans. Prostate cancer risks are lower in Caribbean-origin populations than previously believed, while mortality rates appeared to be higher than reported in African-American men. Studies in Caribbean populations may assist understanding of disparities among African-origin populations with shared heredity.

1. Introduction

Prostate cancer rates are higher in westernized African-origin populations when compared to other ethnic and racial groups [1, 2]. In the United States, prostate cancer remains the principal malignancy in African-American men and the leading cause of cancer-related death in this group [3, 4]. Similar findings have been reported from the English-speaking Caribbean [5], where the majority of the population shares a common heredity with African Americans, as a result of the West African diaspora [6]. Despite the importance of prostate cancer as a cause of ill health and mortality in the Caribbean, there remains limited information about disease rates, risk factors, and the clinical and public health implications for the region [7–10].

The Barbados National Cancer Study (BNCS), funded by the National Institutes of Health, was established in 2002 to document the incidence and risk factors for prostate and breast cancer, among the country's men and women, respectively. Such malignancies are known to be the most frequent among the island's residents [11]. The African-descent Barbados population shares a common heredity with African Americans (but with lower admixture) [12], as well as high rates of lifestyle-related noncommunicable disease [13–16]. While investigation of conditions relevant to African Americans in the US may be confounded by associations with socioeconomic factors, the public care system in Barbados provides easy access to comprehensive healthcare at no cost, thus minimizing such concerns. As demonstrated in our previous work, findings from the Barbadian population may therefore have direct relevance to the health of African-American populations [17].

In addition to collecting data on prostate cancer incidence, a key outcome of the BNCS, we also utilized the established research infrastructure to collect additional information on prostate cancer-related mortality. The purpose of this paper is to present the first comprehensive data about prostate cancer incidence and mortality in Barbados, West Indies, and provide comparisons with African Americans. Although African Americans are consistently reported to

have the highest prostate cancer rates globally, data from Jamaica [8] suggested that Caribbean men might even have higher disease rates. This key clinical and public health concern, underpinned the conduct of this study.

2. Materials and Methods

All histologically confirmed cases of prostate cancer were ascertained from records held at the Pathology Department of the Queen Elizabeth Hospital, Bridgetown, the sole public tertiary care institution on the island, where all pathological specimens are evaluated. Other data sources such as patient charts and pathology reports were also reviewed, and cases of recurrent prostate cancer or disease occurring in non-residents (domiciled for less than 6 months a year) were excluded. Incidence estimates presented here were based on data collected by the BNCS between 2002 and 2008.

To ascertain prostate cancer-related mortality, we reviewed all death certificates for the period January 1, 1995 to December 31, 2008, selecting certificates that listed a diagnosis of prostate cancer alone or in conjunction with other causes of death. Unlike the requirements of the US Standard Certificate of Death, death registration in Barbados during this period did not require physicians to record underlying cause of death.

To address potential overcounting of deaths attributed to prostate cancer [18], we developed a nosological algorithm based on independent review by two clinicians to determine if prostate cancer was (i) unlikely to be the cause of death, (ii) the probable cause (multiple causes of death cited, death likely attributable to metastatic prostate cancer), or (iii) the definite cause (prostate cancer being the single listed cause of death; death attributable to metastatic prostate cancer with other listed conditions unlikely to have directly caused death). Two clinicians (A. J. M. Hennis and D. H.-A. Skeete) resolved any diagnostic discrepancies by consensus.

Informed consent was obtained from all BNCS participants, and the study protocols conformed to the Declaration of Helsinki. In addition, the current study was conducted as a clinical audit of a national dataset on behalf of the Ministry of Health. The data were delinked such that participants could not be identified. This study was approved by the University of the West Indies/Ministry of Health Institutional Review Board.

2.1. Statistical Methods. To calculate crude prostate cancer incidence rates per 100,000 years of observation, we divided the number of incident cases by the number of males (all ages) in the Barbados population and multiplied the results by 100,000. Age-specific incidence rates were calculated in 18 age groups (stratified by 5-year increments as follows: 0–4 years, 5–9 years, 10–14 years, through 85 years, and older). We derived age-standardized rates (with 95% confidence intervals), using the direct method, to allow age-independent comparisons with other studies. These rates were estimated based on three standard populations: the 2000 US standard population [19] and the IARC European and World standard million populations [20]. We also compared age-standardized prostate cancer incidence in Barbados (based on the 2000 US standard population) with US rates (Surveillance Epidemiology and End Results (SEER)) [21], for the period 2002 to 2007, and calculated age-stratified and age-standardized death rates for the period 1995 to 2008. Direct comparisons of prostate cancer incidence in Barbados and the US were made utilizing incidence rate ratios derived from log-linear models, according to age and year of diagnosis. Exact Poisson confidence intervals were calculated for crude and age-stratified rates. Given the utility of the Gamma approximation in providing more accurate estimates with small numbers, we used this method to estimate age-standardized confidence intervals [22].

We used previously described approaches to calculate age-stratified and age-standardized death rates in Barbados for the 14-year period 1995–2008. Because of uncertainty about prostate cancer as an underlying cause of death, we present two mortality rates, based on (i) deaths restricted to those definitely attributed to prostate cancer and (ii) including all deaths, definitely or probably attributed to prostate cancer; deaths unlikely due to prostate cancer were excluded. US cancer mortality information is provided as rates only (without documentation of actual numbers), and stratified by age groups <65 and 65 years and older. Our comparisons with US mortality data (presented in Table 5), are therefore limited by the unavailability of detailed US data. All analyses were carried out using Stata (Version 11, StataCorp LP, College Station, Texas, USA).

3. Results

During the initial six and a half year study period (July 1, 2002–December 31, 2008) of the BNCS, 1,101 men were diagnosed with histologically confirmed prostate cancer. Table 1 presents age-specific prostate cancer incidence in Barbados. Age at presentation ranged from 25 to 99 years, with a median age of 68 years (interquartile range: 61 to 74 years). Prostate cancer incidence increased from 6.0 (95% confidence interval: 1.6–15.3) per 100,000 at ages 40 to 44 years, to a peak of 1,026.6 (95% CI: 898.8–1,167.6) per 100,000 in men aged 70 to 74 years, and declined thereafter. The overall crude incidence rate was 131.0 (95% CI: 123.4–139.0) per 100,000, with rates of 160.4 (95% CI: 151.0–170.2), 163.1 (95% CI: 153.4–173.3), and 112.0 (95% CI: 105.2–119.3) per 100,000 standardized to the US, European, and World populations, respectively. Comparable rates in the US varied according to race, such that overall prostate cancer incidence in African-American and White men was 248.2 (95% CI: 246.0–250.5) and 158.0 (95% CI: 157.5–158.6) per 100,000, respectively.

Figure 1 presents age-specific prostate cancer incidence in Barbadian men and comparable data from the US. Men aged 40–44 years comprised the youngest group which developed prostate cancer and rates were approximately fourfold higher in African Americans (22.9 (95% CI: 21.1–24.9)) than Barbadians (6.0 (95% CI: 1.6–15.3); log linear model comparison, $P = .01$).

Table 1: Age-specific and age-standardized incidence of prostate cancer in Barbados between July 01, 2002 and December 31, 2008, per 100,000 person-years of observation.

Age group (years)	Number of cases	Person-years*	Age-specific rate	95% CI
0–4	0	60,793	0.0	0–6.1
5–9	0	65,446	0.0	0–5.6
10–14	0	65,335	0.0	0–5.7
15–19	0	65,960	0.0	0–5.6
20–24	0	62,648	0.0	0–5.9
25–29	1	68,960	1.5	0–8.1
30–34	0	67,359	0.0	0–5.5
35–39	0	71,536	0.0	0–5.2
40–44	4	66,942	6.0	1.6–15.3
45–49	14	55,952	25.0	13.7–42.0
50–54	79	45,743	172.7	136.7–215.2
55–59	129	30,517	422.7	352.9–502.3
60–64	175	27,778	630.0	540.1–730.6
65–69	203	25,526	795.3	689.6–912.5
70–74	232	22,598	1,026.6	898.8–1,167.6
75–79	147	16,384	897.2	758.0–1,054.5
80–84	74	11,875	623.2	489.3–782.3
85+	33	9,183	359.4	247.4–504.8
Unknown age	10	—	—	
Crude rate	1,101	840,535	131.0	123.4–139.0
Age-standardized rates (US)	—	—	160.4	151.0–170.2
Age-standardized rates (Europe)	—	—	163.1	153.4–173.3
Age-standardized rates (World)	—	—	112.0	105.2–119.3

* 85+ age group rounded up to 9,183 to maintain correct person-year total.

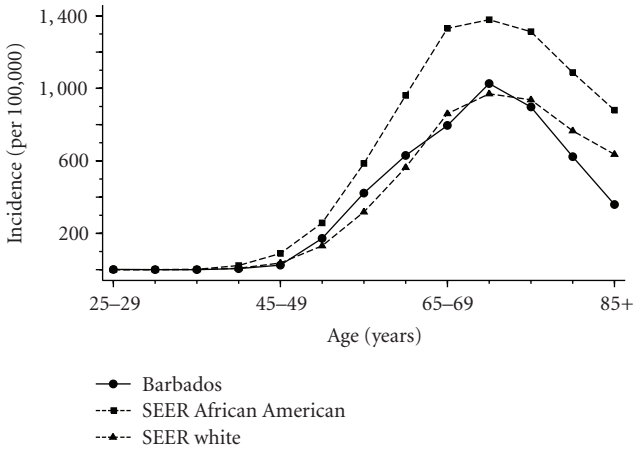

Figure 1: Age-specific incidence of prostate cancer in Barbados (2002–2008) and the US SEER 2000–2007 [21]. Note: SEER incidence rates based on malignant and in situ disease.

The highest prostate cancer incidence among both Barbadians and African Americans occurred among men aged 70–74 years: 1,026.6 (95% CI: 898.8–1,167.6) and 1,378.6 (95% CI: 1,347.4–1,410.3) per 100,000, respectively, still being comparatively higher in the latter group (risk ratio: 1.34, 95% 1.18–1.53, $P < .001$).

Table 2 presents secular trends in incident prostate cancer during the period 2002 to 2008. In contrast to an age-standardized rate of 158.8 (95% CI: 148.6–169.5) per 100,000 among Barbadian men, prostate cancer incidence rates among African Americans always exceeded 225 per 100,000 between 2002 and 2007.

Table 3 presents data on age-specific and age-standardized prostate cancer incidence in Barbadian and African-American men. Incidence rate ratios (IRR) confirmed lower rates of newly diagnosed prostate cancer in Barbadians. Rates among African Americans were approximately 1.5 times higher (among men aged 50 to 79) and in excess of 3.5 times higher among the youngest men (aged 40 to 44 years) ($P < .001$ in all age group comparisons from 45 years and older). Analysis of secular trends in disease incidence during the 6-year period 2002 to 2007 confirmed overall prostate cancer incidence to be between 1.3 and 1.9 times higher in African-American men ($P < .001$ in all annual comparisons).

Table 4 presents age-stratified and age-standardized pros-tate cancer death rates in Barbados between 1995 and 2008, per 100,000 person-years of observation. There were a total of 1,496 death certifications citing prostate cancer as a cause of death. Of these, 943 (63.0%) cited prostate cancer as the only cause of death, and 553 (37.0%) cited one or more other causes. These 553 certifications with multiple causes of death were reviewed by two clinicians, and prostate cancer was determined to either be the probable cause of death (294,

Table 2: Short-term secular change in prostate cancer incidence in Barbados and in African Americans.

Year	Follow-up months (days)	Cases	Person-yrs exposure	Age-standardized incidence rate (SEER US 2000 standard population)	
				Barbados	SEER (African Americans; 17 registries)
2002	6 (183)	78 (77)	64,766	146.3 (115.3–183.3)	273.1 (266.3–280.0)
2003	12 (365)	159 (155)	129,177	151.2 (128.3–177.2)	248.3 (241.9–254.8)
2004	12 (366)	195 (192)	129,530	184.1 (158.9–212.3)	245.2 (238.9–251.6)
2005	12 (365)	167 (166)	129,177	159.3 (135.9–185.7)	227.1 (220.9–233.4)
2006	12 (365)	135 (135)	129,177	127.3 (106.7–150.9)	225.8 (220.0–231.7)
2007	12 (365)	188 (187)	129,177	178.2 (153.5–205.9)	227.8 (222.1–233.7)
2008	12 (366)	179 (179)	129,530	169.3 (145.3–196.3)	*n/a**
2002–2007	66 (2,009)	922 (912)	711,004	158.8 (148.6–169.5)	248.2 (246.0–250.5)
2002–2008	78 (2,375)	1,101 (1,091)	840,535	160.4 (151.0–170.2)	—

SEER rates based on malignant and in situ disease.
*SEER data for 2008 not available (*n/a*).

Table 3: Incidence rate ratios (IRRs) comparing age-specific incidence rates and secular incidence rates between Barbados and the United States (SEER 17 registries; African Americans) [6].

Characteristic	IRR	95% CI
Age[1]		
40–44	3.84	1.43–10.25
45–49	3.57	2.11–6.05
50–54	1.49	1.20–1.87
55–59	1.39	1.16–1.65
60–64	1.53	1.31–1.77
65–69	1.67	1.46–1.92
70–74	1.34	1.18–1.53
75–79	1.46	1.24–1.72
80–84	1.74	1.38–2.20
85+	2.45	1.73–3.46
Year[2]		
2002	1.87	1.50–2.34
2003	1.69	1.44–1.98
2004	1.34	1.16–1.55
2005	1.45	1.24–1.69
2006	1.77	1.50–2.11
2007	1.30	1.12–1.50

[1] Age-specific incidence rate ratios calculated for ages 40–44 and older—below age 40 there was just one case of prostate cancer in Barbados.
[2] Annual incidence rate ratios calculated for ages 40–44 and above using Poisson regression, adjusted for age. IRRs based on unadjusted *crude rates* are (2002) 1.35 (1.08–1.69), (2003) 1.26 (1.07–1.48), (2004) 1.01 (0.88–1.17), (2005) 1.12 (0.96–1.31), (2006) 1.43 (1.20–1.69), (2007) 1.06 (0.92–1.23).

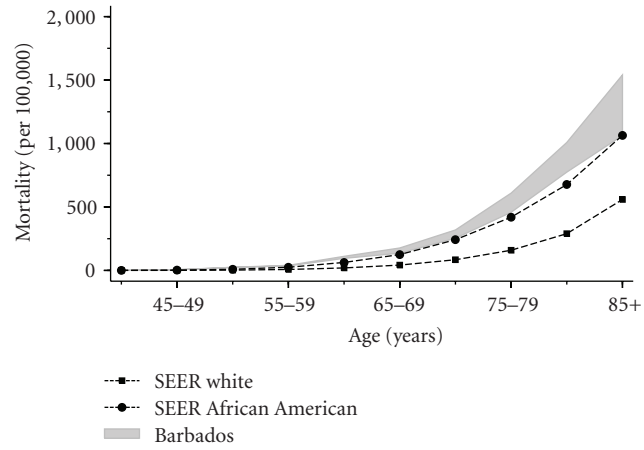

Figure 2: Age-specific death rates of prostate cancer in Barbados (1995-2009) (The band representing the distribution of age-specific mortality is composed of "definite" (lower limit) and "definite and probable" (upper limit) prostate cancer mortality.) and the US SEER 2002–2006.

19.7% of all deaths) or not likely to be the cause of death (259, 17.3% of all deaths).

The number of deaths from prostate cancer progressively increased with age, with the distribution of definite prostate cancer mortality by 10-year age groups being 1 or 0.1% (aged 39 or less), 7 or 0.7% (aged 40–49), 25 or 2.6% (aged 50–54), 25 or 2.6% (aged 55–59), 61 or 6.5% (aged 60–64), 80 or 8.5% (aged 65–69), 132 or 14% (aged 70–74), 173 or 18.3% (80–84), 225 or 24% (aged 85+). Comparable combined probable and definite prostate cancer mortality by 10-year age groups were 1 or 0.1% (aged 39 or less), 7 or 0.6% (40–49), 54 or 4.4% (50–59), 175 or 14.1% (60–69), 396 or 32.0% (70–79), 602 or 48.7% (80 years and older). The crude death rate for definite prostate cancer deaths was 48.6 (95% CI: 45.5–51.8) per 100,000 and for definite and probable prostate cancer deaths, 63.7 (95% CI: 60.2–67.3) per 100,000.

The equivalent age-standardized rates (US standard 2000 population) were 62.7 (95% CI: 58.8–66.9) deaths per 100,000 person-years for definite prostate cancer deaths and 82.7 (95% CI: 78.1–87.4) per 100,000 for combined definite and probable prostate cancer deaths.

Figure 2 and Table 5 present data comparing mortality from prostate cancer in the Barbadian and US populations between 1995 and 2008. In Barbados, overall prostate cancer mortality (probable and definite) ranged from 63.2 to 101.6 per 100,000, while overall rates among African Americans

Table 4: Age-stratified and age-standardized definite and probable death rates from prostate cancer in Barbados between Jan 01, 1995 and Dec 31, 2008, per 100,000 person-years of observation.

Age group (years)	No. of definite/(probable and definite) prostate cancer deaths	Person-years	Mortality Definite prostate cancer death (95% CI)	Mortality Definite and probable prostate cancer deaths (95% CI)
0–4	0	140,154	—	—
5–9	0	150,870	—	—
10–14	0	150,615	—	—
15–19	0	152,055	—	—
20–24	0	144,420	—	—
25–29	0	158,970	—	—
30–34	1	155,280	0.6 (0–3.6)	0.6 (0–3.6)
35–39	0	164,910	—	—
40–44	0/0	154,320	—	—
45–49	7/7	128,985	5.4 (2.2–11.2)	5.4 (2.2–11.2)
50–54	25/26	105,450	23.7 (15.3–35.0)	24.7 (16.1–36.1)
55–59	25/28	70,350	35.5 (23.0–52.5)	39.8 (26.4–57.5)
60–64	61/71	64,035	95.3 (72.9–122.4)	110.9 (86.6–139.9)
65–69	80/104	58,845	136.0 (107.8–169.2)	176.7 (144.4–214.1)
70–74	132/166	52,095	253.4 (212.0–300.5)	318.6 (272.0–371.0)
75–79	173/230	37,770	458.0 (392.3–531.6)	608.9 (532.8–692.9)
80–84	212/276	27,375	774.4 (673.7–866.0)	1,008.2 (892.8–1,134.5)
85+	225/326	21,165	1,063.1 (928.7–1,211.4)	1,540.3 (1,377.6–1,716.9)
Age unknown	2/2	—	—	
Total	943/1,237	1,937,664		
Crude rate			48.6 (45.5–51.8)	63.7 (60.2–67.3)
Age-standardized rates (US)	—	—	62.7 (58.8–66.9)	82.7 (78.1–87.4)
Age-standardized rates (Europe)	—	—	49.6 (46.4–53.0)	64.3 (60.7–68.2)
Age-standardized rates (World)	—	—	29.7 (27.7–31.9)	38.1 (35.8–40.6)

ranged from 51.1 to 78.8 per 100,000. During the period 1995 to 1998, overall rates of "definite" prostate cancer mortality in Barbados were lower than reported in African Americans (52.3–67.7 and 72.8–78.3 per 100,000, resp.). In contrast, mortality rates in Barbados due to definite prostate cancer between 1999 and 2006 (barring the year 2001) were consistently higher than those reported in African Americans, who demonstrated a trend to declining related mortality. With regards to age-stratified, Barbadian men aged less than 65 years had higher mortality attributed to definite prostate cancer than African Americans (except for 1998 and 2003). Among men aged 65 years and older, death rates attributable to probable and definite prostate cancer were higher among older Barbadian men between 1998 and 2006. Figure 2 compares age-specific prostate cancer mortality, rates in White and African Americans, with Barbadians. Based on "definite" prostate cancer-related deaths, age-specific mortality rates in Barbados were at least as high as those in African Americans for all age groups and higher when prostate cancer was considered the combined "definite and probable" cause of death. Mortality increased with older age in each of the three ethnic groups.

4. Discussion

A total of 1101 incident prostate cancer cases were recorded in Barbados during the six and a half year study period (July 2002 to December 2008), for an incidence rate of 160.4 per 100,000 (standardized to the US population). This prostate cancer incidence was similar in Barbadian and White American men, in contrast to rates in African-American men, which were about one and a half times higher. The age-specific pattern of incident disease was similar in both African-descent groups, rising to a peak by ages 70 to 74 years, and declining thereafter. Younger African-American men aged 40 to 44 years, however, experienced a nearly fourfold higher occurrence of prostate cancer than similarly aged Barbadian men (groups based on relatively low numbers). While overall prostate cancer mortality rates

Table 5: Annual age-standardized definite and probable death rates from prostate cancer in Barbados compared to US SEER data (African Americans) between Jan 01, 1995 and Dec 31, 2009, per 100,000 person-years of observation.

Year	Prostate cancer death rates					
	Barbados[1]			SEER (African Americans)		
	All	<65 years	65+ years	All	<65 years	65+ years
1995	67.7/82.9	6.7/7.9	489.5/602.0	78.2	6.7	572.5
1996	52.3/63.2	7.6/8.6	361.2/440.4	78.8	6.5	579.2
1997	66.8/72.7	10.8/10.8	453.6/500.4	74.3	6.3	544.2
1998	61.4/74.8	4.2/4.2	457.1/562.9	72.8	6.3	532.4
1999	72.5/84.7	8.5/8.5	514.3/611.1	70.1	5.8	514.8
2000	70.5/86.2	9.5/10.6	491.9/609.4	68.7	5.4	505.8
2001	60.5/81.4	10.1/13.3	408.3/552.4	66.5	5.4	488.9
2002	78.7/88.8	10.8/10.8	548.4/628.2	63.0	5.4	461.2
2003	63.7/84.5	3.2/5.2	481.8/632.3	58.0	5.4	421.4
2004	63.4/85.4	6.2/7.4	458.7/625.4	56.2	5.0	410.4
2005	64.7/92.7	8.4/8.4	454.0/675.0	54.2	5.0	393.8
2006	53.2/75.4	11.5/13.7	341.4/501.8	51.1	4.8	371.0
2007	50.8/74.0	12.6/13.6	315.4/491.3	*n/a*[2]	*n/a*[2]	*n/a*[2]
2008	61.9/101.6	8.8/10.9	428.9/728.2	*n/a*[2]	*n/a*[2]	*n/a*[2]
2009	52.8/91.4	7.2/7.2	368.3/673.3	*n/a*[2]	*n/a*[2]	*n/a*[2]

[1] All death certificates have been independently reviewed by two clinicians. We report two rates, where prostate cancer has been classified as a definite cause of death/and combined definite or probable cause of death.
[2] Mortality data for 2007 to 2009 not available (*n/a*).

demonstrated a clear decline in African Americans during the period from 2000 to 2006, they were higher in Barbadian men.

Prostate cancer ranks as the sixth most frequent incident tumor worldwide, accounting for nearly 10% of all cancers in men [23]. Prevalence is higher in developed than developing countries, where 15% and 4% of men are affected, respectively.

There are clear associations between prostate cancer occurrence and race (or ethnicity) such that African-American men experience the highest rates globally, Caucasian men in North America and Europe, high and intermediate rates, while Asian men have relatively low disease rates [1, 23, 24]. Based on comprehensive global population-based cancer data reported continuously over a 20-year period by the International Agency for Research in Cancer (IARC), the highest prostate cancer incidence and mortality worldwide was documented in African-American men [1]. Incidence and mortality rates in African-American men were approximately sixty times and twelve times, respectively, those recorded in Chinese men (known to be at lowest risk).

Few data exist on prostate cancer rates in West African and Caribbean populations who share a common heredity with African-American populations. Much of the currently available data have been reported from the Globocan database, often the only source of cancer data from many regions of the world [5]. It is important to note that the authors caution that the "degree of detail and quality of the data vary considerably" and provide the caveat that the quality of information presented depends "on the extent and accuracy of locally available data." While there are extensive data on prostate cancer rates among African-American populations, few data are available for West African populations, who are thought to have relatively high disease rates [25].

Prostate cancer is listed as the second most frequent malignancy among West African men with rates of approximately 19 per 100,000 [26]. Two independent hospital-based studies conducted in Nigeria reported prostate cancer incidence rates of 61.3 per 100,000 and 127 per 100,000 [27, 28]. However, a critical reappraisal by Ben-Shlomo et al. highlighted major errors in these estimates [29]. Their revised calculations reduced these estimated incident rates to 6.1 per 100,000 and 21.1 per 100,000, respectively. Ben-Shlomo et al. similarly recalculated prostate cancer incidence reported in a hospital-based case series conducted in Cameroon at 0.2 per 100,000 [29], rather than the reported rate of 93.8 per 100,000 [30]. These hospital-based studies conducted in the 1980s to mid 1990s would have led to erroneous estimates of cancer incidence and reevaluation of these data provides evidence for relatively low prostate cancer rates in West Africa.

Further evidence of relatively low prostate cancer incidence rates in West Africa comes from cancer registry data from Guinea (8.1 per 100,000), Mali (6.3 per 100,000), and Gambia (1.2 per 100,000) a decade and a half ago [31, 32].

Information is now available from studies of first generation Black Caribbean and African men resident in the United Kingdom. Risk of incident prostate cancer was three times higher in African Caribbean compared to European men resident in North East London [33]. The larger Prostate Cancer in Ethnic Subgroups (PROCESS) study of incident

prostate cancer conducted in London and Bristol over a longer (5-year) period documented adjusted rates (based on the European standard population) of 173.1 per 100,000 for Black Caribbean men and 139.3 per 100,000 for Black African men, compared to 56.4 per 100,000 in White British men [29]. Standardized to the US population, prostate cancer incidence was 166 per 100,000 among Black British men, inline with the rate of 158.9 per 100,000 among Barbadian men.

4.1. Prostate Cancer Incidence in the Caribbean. The comparatively lower rates of prostate cancer in Barbadian men contrasts with earlier reports from Jamaica, West Indies, where the reported average incidence rate of 304 per 100,000 (1989 to 1994) exceeded comparable rates in African-American men (249 per 100,000) [8]. The accuracy of the Jamaican rates has also been challenged by Ben-Shlomo et al., who estimated the corrected prostate cancer incidence (unadjusted) to be less than one-fourth the original rate at 70 per 100,000 [29]. They suggested that standardization of these rates to the US population would reduce this estimate even further, given the comparably younger average age of the Jamaican population. Based on data from the largely urban-based Jamaica Cancer Registry, Hanchard et al. [7] and Gibson et al. [10] reported standardized prostate cancer incidence rates (world population) of 56.4 and 65.6 per 100,000, respectively, over consecutive 4-year periods, (1993 to 1997 and 1998 to 2002). These rates are entirely consistent with those estimated by Ben-Shlomo et al. [29].

Limited data on prostate cancer incidence are available from the French Caribbean islands, which also have predominantly West African-origin populations. There has been an active cancer registry in Martinique since 1983, and Dieye et al. [34] reported a cumulative age-standardized (world population) prostate cancer incidence of 80.8 per 100,000 (between 1981 and 2000). Annual rates increased over time to 161 per 100,000 in 2000, comparable to rates in Barbados. Prostate cancer incidence was also similar in Guadeloupe at a rate of 168 per 100,000 [35]. Based on registry reports, prostate cancer rates (standardized to the world population) were relatively lower in Cuba (Hispanic Caribbean: 34.9 per 100,000 in 1999) [36].

In sum, prostate cancer incidence is similar in Black Caribbean populations resident in the United Kingdom and French and Barbadian populations resident in the Caribbean, and is around the order of 160 per 100,000. This is in sharp contrast to earlier reported incidence rates of around 300 per 100,000 from Jamaica, which appear to be an overestimate. Our findings, supported by other reports, therefore indicate that the impression of the Caribbean being a high-risk region for prostate cancer is incorrect.

The impact of screening must be specifically addressed, as it significantly influences prostate cancer incidence. Increased utilization of prostate-specific antigen (PSA) screening and higher uptake of transurethral prostatic resection significantly contributed to increased prostate cancer rates in the US [37–39]. Anecdotally, PSA screening in the Caribbean region still lags behind uptake in more developed regions. Bunker et al. reported a prevalence of 10% for screen-detected prostate cancer in Tobago, West Indies [9], which highlights the potential impact of increased utilization of screening on disease rates.

4.2. Prostate Cancer Mortality. Cancer is now the second leading cause of death in the US accounting for 1 in 4 deaths [40, 41]. Racial disparities in cancer mortality persist in the US, although survival has improved in virtually all ethnic groups [3]. As such, survival after a cancer diagnosis still remains poorer among Black than White Americans [42]. Prostate cancer mortality has been approximately two times higher among Black than White Americans in recent decades [43], and current global comparisons confirm worse mortality outcomes in African-American men [24]. Vital statistics from the UK indicate that prostate cancer mortality rates among men born in West Africa and the West Indies are two to three times higher than overall rates in the male population [2]. Limited data also confirm lower 5-year survival among Black than White men following a prostate cancer diagnosis [44].

Factors expected to affect outcomes, such as preexisting comorbid conditions and access to care or uptake of PSA screening, did not emerge as independent predictors of ethnic disparities in prostate cancer mortality in a recent meta-analysis [45]. These findings must, however, be viewed with caution, given the substantial body of information to the contrary [46–48]. Tumor grade (biological aggressiveness) [49], underpinned by specific genetic differences [50], may partly explain racial disparities in prostate cancer mortality.

Mortality rates following a prostate cancer diagnosis in recent years are at least similar, in Barbadian and African-American men (and to some extent higher in the former group). This finding is a cause for concern, given the comparatively lower prostate cancer incidence in Barbados.

A unique strength of this study concerns the access to all histologic samples analyzed at the island's sole pathology department, leading to near complete ascertainment of all incident prostate cancer cases. The strict criteria we used to establish a diagnosis of prostate cancer, which required histological confirmation, would have however reduced the true number of cases, as standard practice includes observation or empiric treatment of elderly men without proceeding to biopsy. This practice would have resulted in an underestimate of prostate cancer incidence in this study. While information about the uptake of biopsy in the diagnosis of prostate cancer nationally would have been useful, this was beyond the scope of this study. It is also our view that there is a lower uptake of PSA screening in Barbados compared to the US, which coupled with lower biopsy rates would have also led to an underestimate of prostate cancer incidence. The majority of the Barbadian population is of African descent, with fewer than 5% of men self-reporting White race (2000 household census). This low percentage of non-African descent Barbadians is likely to have minimal effect on our prostate cancer rates and allows comparison with other similar populations.

A potential limitation is that differences in death certification processes would have affected the comparability of prostate cancer mortality rates in Barbados versus the United States. We therefore developed an algorithm to classify prostate cancer-related deaths. This algorithm used an extremely conservative approach, with death only attributed to prostate cancer, where it was listed as the only cause, or the death certificates provided clear evidence of death due to metastatic prostate cancer. This methodology would have likely led to underestimates of prostate cancer as a "definite" cause of mortality and reduced related mortality rates accordingly. This research was based on comprehensive access to information that allowed identification, for the first time, of all incident prostate cancer cases and deaths occurring on the island, although the caveats noted would have to be considered in the interpretation of our findings.

5. Conclusions

This paper describes the incidence and mortality from prostate cancer in Barbados, West Indies, mainly populated by individuals of West African descent. Incidence rates were found to be consistent with those of similar populations in the Caribbean, as well as Caribbean populations in the United Kingdom, and lower than rates reported in African Americans. In spite of easy access to comprehensive health care, freely available in the public sector, prostate cancer mortality was comparatively higher than rates experienced by African-American populations. This observation calls for clinical and public health approaches to improve detection of disease, in order to reduce the high mortality rates currently experienced.

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Review Article

Environment as a Potential Key Determinant of the Continued Increase of Prostate Cancer Incidence in Martinique

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Prostate cancer incidence is steadily increasing in many developed countries. Because insular populations present unique ethnic, geographical, and environmental characteristics, we analyzed the evolution of prostate cancer age-adjusted world standardized incidence rates in Martinique in comparison with that of metropolitan France. We also compared prostate cancer incidence rates, and lifestyle-related and socioeconomic markers such as life expectancy, dietary energy, and fat supply and consumption, with those in other Caribbean islands, France, UK, Sweden, and USA. The incidence rate of prostate cancer in Martinique is one of the highest reported worldwide; it is continuously growing since 1985 in an exponential mode, and despite a similar screening detection process and lifestyle-related behaviour, it is constantly at a higher level than in metropolitan France. However, Caribbean populations that are genetically close to that of Martinique have generally much lower incidence of prostate cancer. We found no correlation between prostate cancer incidence rates, life expectancy, and diet westernization. Since the Caribbean African descent-associated genetic susceptibility factor would have remained constant during the 1980–2005, we suggest that in Martinique some environmental change including the intensive use of carcinogenic organochlorine pesticides might have occurred as key determinant of the persisting highly growing incidence of prostate cancer.

1. Introduction

Prostate cancer incidence is steadily increasing in many developed countries, where it is commonly attributed to improvement in screening detection and to population ageing [1]. We have previously analysed these two factors [2], and in response to a recent article [3], we have argued that overdiagnosis by the routine use of prostate-specific antigen (PSA) test cannot fully account for the growing incidence of this cancer [4]. Furthermore, increase in life expectancy does not explain why overall the rise of cancer incidence affects all age categories [5] and why it occurs earlier in life [6].

In a previous multifactorial study, we have suggested that in the two French Caribbean islands, Martinique and Guadeloupe, prostate cancer may in fact be caused by environmental factors and that among these factors, carcinogenic organochlorine pesticides may play a role [7].

In this paper, we further attempt to show that in Martinique, environmental change may account for the growing incidence of prostate cancer in highly susceptible people and discuss the role of exogenous carcinogens that may be involved.

2. Material and Methods

Because insular populations present unique ethnic, geographical, and environmental characteristics that may be well conserved, studies of populations of the Caribbean can help elucidate the aetiology of prostate cancer. We have chosen the tropical island Martinique, in the French West Indies, because of its limited territory (1128 km^2), its low number of inhabitants (414 516), a medical practice and lifestyle-related behaviour that does not differ from metropolitan France,

the availability of a cancer registry rigorously collecting and reporting cases, and the possibility of determining environment- and lifestyle-related factors and their time-related modifications.

In this ecological study, we have analysed the evolution of prostate cancer incidence rates in Martinique in comparison with that in metropolitan France during the period 1980–2005 and have compared the incidence rates obtained in 2005 with those of other Caribbean islands and of UK, Sweden, and USA. Data collection was done as follows: for Martinique, we used data from the Martinique cancer registry held by AMREC, the Martinique Association for Epidemiological Research on Cancer [8]. For comparison with metropolitan France, we used data from the French National Sanitary Surveillance Institute (InVS) [9], which provides incidence rates from 11 metropolitan "department" registries. These registries are those from which the national extrapolated incidence rates of prostate cancer in metropolitan France are based on. For international comparison, we used incidence rates from the Globocan 2008 database of the international Agency for Research on Cancer (IARC) [10]. However, since these data may have been highly extrapolated, we also used for comparison data collected by specific registries including the one of the public health ministry of Cuba [11], for UK, that is, for England, Scotland, and Wales, those from the Office for National Statistics [12], the Information Services Division, Scotland [13], and the Welsh Cancer Intelligence and Surveillance Unit [14], and for Sweden, USA, and metropolitan France, those from the National Board of Health and Welfare [15], the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) [16], and the InVS [9], respectively. Finally, in order to make data comparison, we only considered incidence rates that had been age-adjusted to the IARC world standard and expressed as age-standardized rates (ASR). Since in Martinique PSA screening does not differ from metropolitan France, data processing consisted of comparing the evolution of prostate cancer incidence rates in Martinique with that of metropolitan France. Furthermore, in order to determine the best model fitting incidence growth curves, we checked for growth homogeneity for each of the 11 metropolitan French "department" registries and for the registry of Martinique. For modeling, we used a least-square regression analysis and established curve equations according to the best values obtained for the determination coefficient R^2. Since the best model fits in exponential functions, data were linearized by log transformation. For comparison of the two groups, the interaction between group and time was analyzed by a mixed linear model, assuming an unstructured covariance matrix for the random effects and a first-order autoregression covariance structure for the within population correlation. Slopes were treated as random effect, thus the intercept at year 1985 is interpretable as initiation of growth, and the slope is interpretable as rate of growth for each population. Mathematical treatments were done using contrasts of fixed effects for the group slopes with inference based on the F-test. Estimation by restricted maximum likelihood (REML) was computed using SPSS v.16.0 (SPSS, Inc., Chicago, Ill, USA), and model suitability was assessed by Akaike's information criterion. Coefficients, confidence intervals (CI) of coefficients, and two-sided P values are reported for the model. Since it has been shown that due to some ethnographic genetic factor, there is a marked increase in prostate cancer incidence in African descents and because Caribbean people are African descents, for international comparison, we took into account the percentage of African descents in Caribbean, UK, and Sweden in the Encyclopedia of the Nations [17], the Office by National Statistics [18], and the Befolkningsstatistik [19], respectively. Unfortunately, due to legal regulation, data were not available for metropolitan France, but a common estimation is that this percentage is low and supposed to be not different from the percentage in UK and Sweden. We also considered a report from the French ministry of health indicating that the health care system in Martinique and Guadeloupe does not differ to that in metropolitan France [20]. In addition, we used several usually accepted socioeconomic markers of lifestyle-related behaviour, such as life expectancy at birth and food supply and consumption in order to make comparison. For comparing life expectancy at birth, we used data source from the WHO Core Health Indicators database for 2006 [21], and for comparing dietary energy and fat supply and dietary energy and fat consumption, we used data source from FAO Food Balance Sheets 1988–1990 [22] and data source from FAO Statistical Yearbook 2009 [23], respectively. We also used data from Eurostat [24] and from US-EPA [25] for pesticide use and exposure in the different countries or territories analyzed for which specific incidence registries were available. For Martinique, we used the determination we had previously made [7]. For determination of the correlation coefficient, r, we used the Spearman test.

3. Results

Tables 1 and 2 and Figures 1 and 2 summarize our data. As indicated in Table 1, the world age-standardized incidence rate of prostate cancer in 2005 in Martinique is one of the highest worldwide whatever it has been determined from the Martinique specific registry of AMREC or estimated from the IARC Globocan 2008 database: 177 per 100 000 according to the AMREC registry and 173.7 per 100.000 according to the IARC Globocan database. This incidence rate is indeed higher than those obtained from specific registries for metropolitan France, Sweden, and USA and much higher than the ones reported for UK. However, surprisingly, despite the fact that with the exception of Cuba and Trinidad and Tobago, 80 to 95 percents of the Caribbean population are of African origin, as it is the case in Martinique, this incidence rate was found to be much higher than those reported by IARC in the Globocan 2008 database for Guadeloupe and other Caribbean islands and even higher than the one reported in 2003–2007 for African descents living in the USA.

The growth curves of prostate cancer incidence rates expressed as ASRs during the period 1980–2005 (i.e., during one generation), respectively, for Martinique, for the 11 metropolitan "department" registries and for overall metropolitan France are displayed Figures 1 and 2. We found that the overall growth rate of incidence in Martinique as well

Table 1: World age-standardized incidence rates (ASRs) of prostate cancer in 2005 in Caribbean, USA, UK, Sweden, metropolitan France, and Martinique. Comparison with percentages of African descents, life expectancy at birth, dietary energy and fat supply, and dietary energy and fat consumption.

Region	ASR 2005 specific registries[a]	ASR Globocan 2008[b]	African descents[c] (%)	LEB[d] (years)	DES (kcals)[e]	FS (g/person/day)[f]	DEC (Cal/person/day)[g]	FC (g/person/day)[h]
Caribbean								
Jamaica	—	*51.1*	90.9	69	2 558	68	2 808	84
Cuba	**29.8**	*53.8*	11	78	3 129	83	3 275	54
Dominican Republic	—	*68.8*	84	66	2 310	60	2 298	77
Haiti	—	*78.4*	95	59	2 006	38	1 835	31
Bahamas	—	*78.5*	85	71	2 776	91	2 690	93
Trinidad and Tobago	—	*89.4*	39.5	66	2 770	71	2 759	77
Guadeloupe	—	*94.8*	90	76	2 776	84	—	—
Puerto Rico	—	*102.2*	—	—	—	—	—	—
Barbados	—	*140*	80	72	3 217	111	2 926	88
USA total	**106**	*83.8*	12.6	75	3 642	154	3 826	164
Black	164.8	—		—	—		—	—
White	101.8	—		—	—		—	—
UK	**52.2**[i]	*62.1*	2	77	3 270	142	3 426	137
Sweden	**112.4**	*114.2*	1.1	79	2 977	127	3 120	123
metropolitan France	**121.2**	*118.3*	N/A	77	3 593	168	3 602	164
Martinique	**177**	*173.7*	80	76.5	2 768	84	—	—

[a]Age-standardized rates (ASR) are per 100 000 man-year and are age-adjusted to the IARC world standard population. Data source are obtained for Cuba from the Public Health Ministry [11], for USA, from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) 2003–2007 [16], for UK, from the Information Services Division [12], Scotland [13] (see i), for Sweden, from the National Board of Health and Welfare [15], for metropolitan France, from the French National Sanitary Surveillance Institute (InVS) [9], and for Martinique, from AMREC [8].
[b]Data source for World ASR obtained from Globocan 2008 [10].
[c]Data source obtained from the Encyclopedia of the Nations [17], the Befolkningsstatistik [19], and the Office by National Statistics [18], for the Caribbean area, Sweden, and UK, respectively. The Caribbean people living in UK represent 1% of the overall population. For France, data are not available (N/A) for ethical considerations and legal regulation. Values are also supposed to be low, within the same range as what is estimated for Sweden and UK.
[d]Life expectancy at birth (LEB) (males). Data source obtained from the WHO Core Health Indicators for 2006 (WHO World health statistics, 2008).
[e]Dietary energy supply (DES), average total kilocalories available per person per day for the period 1988–1990. Data source obtained from FAO food balance sheets. National indices of dietary fat supplies [18, 22].
[f]Fat supplies (FS) are expressed as average grams of fat available per person per day for the period 1988–1990. Data source obtained from FAO food balance sheets. National indices of dietary fat supplies [18, 22].
[g]Dietary energy consumption (DEC) (Cal/person/day) for the period 2003–2005. Data source obtained from FAO Statistical Yearbook 2009 [19, 23].
[h]Fat consumption (FC) (g/person/day) for the period 2003–2005. Data source obtained from FAO Statistical Yearbook 2009 [19, 23].
[i]ASR 2005 determined from specific registries for the whole UK are not available. World ASR are 61.6 for England in 2002 and 52.2 for Scotland in 2005. Europe-ASR for England, Wales and Scotland in 2005 are 95.6, 112.9 and 79.6, respectively.

as in metropolitan France is constant. Evaluation of the correlation between incidence ASRs and time confirmed indeed that both incidence growth curves fit in well an exponential function: mean $r = 0.993$ for Martinique and mean $r = 0.990$ for metropolitan France, with incidence growth curve equations in the form of $y = 2E - 53e^{0.063x}$ and of $y = 6E - 50e^{0.0589x}$ for Martinique and metropolitan France, respectively. No significant difference could be detected in the interaction of time by incidence rates for Martinique compared to metropolitan France ($F_{1,18.2} = 0.68$, $P = 0.4$). In other words, after log transformation, when compared to metropolitan France the overall growth rate of incidence of prostate cancer for Martinique is not significantly different ($\beta = -0.004$, $P = 0.4$, 95%, CI -0.013 to 0.006). However, as displayed in Figure 2, the incidence rates for Martinique are significantly at a constant higher level than those for metropolitan France (0.416, $P < 0.001$, 95% CI 0.294 to 0.539). Table 1 also indicates that life expectancy at birth in Martinique and Guadeloupe is similar to that in France, UK, Sweden, and USA. By contrast, with the exception of Cuba, life expectancy at birth in the Caribbean islands other than Martinique and Guadeloupe is generally lower, in the range of 59 to 72 years of age. We found no correlation between prostate cancer incidence rates and life expectancy at birth ($r = 0.239$, $P = 0.4$), and similarly, as far as diet westernization is concerned, no correlation between prostate cancer

Table 2: Amounts of pesticides used in Martinique (in tons) in comparison with metropolitan France and other countries. Search for a correlation with the incidence rates of prostate cancer.

Region	Total amount[a,b]	Population[b]	Amount per inhabitant	ASR 2005[c]
Cuba	1 900	11 477 459	$1 \cdot 10^{-4}$	29.8
Sweden	1 553	9 074 055	$1 \cdot 10^{-4}$	112.4
UK	15 248	62 348 447	$2 \cdot 10^{-4}$	52.2
metropolitan France	89 084	63 136 180	$1.4 \cdot 10^{-3}$	121.2
USA	555 300	310 232 863	$1.7 \cdot 10^{-3}$	106
Martinique	2 500	414 516	$6 \cdot 10^{-3}$	177

[a]Amounts are expressed in tons.
[b]Values are indicated for 2000.
[c]Data from specific registries. See Table 1

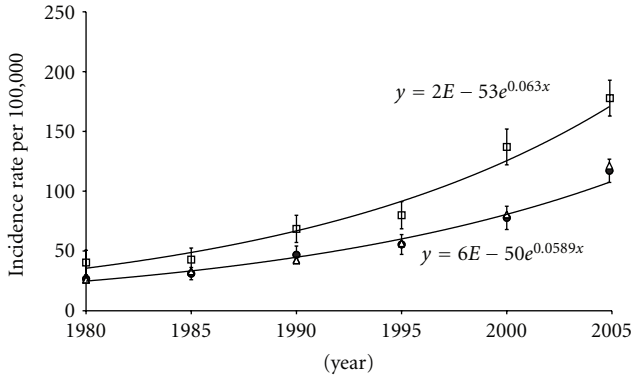

Figure 1: Evolution of prostate cancer incidence rates expressed as ASRs in Martinique □ in comparison with the incidence growth curve obtained from the 11 "department" registries of metropolitan France • and with the extrapolated overall incidence growth curve for metropolitan France △. Values of R^2 were 0.9742 for Martinique and 0.9845 for the 11 metropolitan "department" registries. Note that for Martinique and metropolitan France, despite the fact they are seemingly diverging since 1985, after log transformation, the 2 curves are not significantly diverging (see Figure 2).

incidence rates as determined by Globocan 2008 and dietary energy (expressed in calories) and fat consumption as determined by FAO (for calories: $r = 0.235$, $P = 0.4$, for lipids: $r = 0.4$, $P = 0.1$). However, when analyzing the pool of all countries or territories included in the study (see Table 1), we found a strong correlation between life expectancy and dietary energy and fat intake ($r = 0.911$, $P = 0.001$). Moreover, as suggested in Table 2, except for Sweden for which factors other than pesticides should be considered, we found some degree of correlation between the incidence rate of prostate cancer and the level of pesticide use in the different countries and territories analyzed, the higher the level is, the higher the prostate cancer incidence tends to be ($R^2 = 0.67$, $P = 0.04$).

4. Discussion

Despite the fact that prostate cancer is the most frequent diagnosed cancer and the second cause of cancer death in men in Western countries, its aetiology remains unclear. The only established risk factors are advancing age, family history, and ethnic origin [26]. However, risk factors are not necessarily cancer causing agents, that is, agents directly involved in the carcinogenesis process, but most often familial factors that contribute to genetic susceptibility and/or lifestyle-related factors that contribute to exposure to carcinogens and/or cocarcinogens [27]. Moreover, although environmental causes of prostate carcinogenesis have not yet been clearly established [26, 28], prostate cancer, as other cancers, is believed to result from a multifactorial process involving both genetic and environmental components [29, 30].

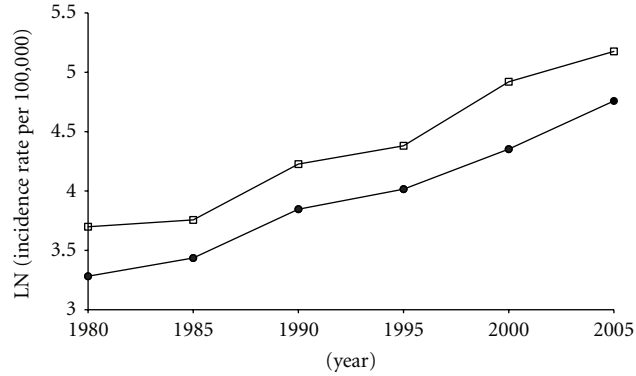

Figure 2: Evolution of Log transformed prostate cancer incidence rates expressed as ASRs for Martinique and metropolitan France. Incidence rates in Martinique are continuously at a higher level than in metropolitan France ($P < 0.001$).

A major finding in the present study is that in Martinique, the incidence rate of prostate cancer is presently one of the highest reported worldwide (e.g., even higher than the one for the black people living in USA) and that it is continuously growing since 1985 in an exponential mode, at a growth rate not differing from that of metropolitan France (i.e., the initial difference remains constant) but that it is constantly at a higher level that differs significantly from that of metropolitan France, meaning that after log transformation, the two incidence growth curves are parallel. A similar trend in the continuously growing incidence rate of prostate cancer is reported in several countries in Europe, including Denmark, Finland, Norway, Sweden, Ireland, and The Netherlands [10, 31]. However, this trend is not observed in the USA, since after the prostate cancer incidence rate peaked in 1992, there is in this country for still undetermined reasons a decrease in prostate cancer incidence although the incidence rate in 2007 remains at a higher level than it was in 1975 [32].

In response to a recent published study carried out in the USA concerning prostate cancer diagnosis and treatment after the introduction of PSA screening [3], we have already discussed the fact that the introduction two decades ago of PSA-based screening techniques cannot explain the persisting growing incidence of prostate cancer in many developed countries [4]. Indeed, exponentially growing incidence rates, such as those reported in Figures 1 and 2 with no visible inflexion, tend to confirm our previous hypothesis according to which, in addition to screening, other factors should be considered, accounting for the continuously growing incidence

Table 3: CMR and presumed CMR pesticides used in Martinique.

	On the market	Maximum of use	Withdrawal from the market for agricultural use	Continuation of use	IARC classification
Technical DDT	1939	1960–1990	1972	—	2B
Technical HCH	1940[a]	1950–1960	1988	1998	2B
Lindane	1940[a]	1950–1960	1992	—	2B
Aldrin/dieldrin	1950[a]	1960	1972	1992	3[b]
Chlordecone	1972	1980	1990	1993	2B
Chlordanes	1960[a]	—	—	—	2B
Simazine	1991[a]	—	2001	—	3[b]

[a]: Official data not available [b]: Aldrin, Dieldrin, and Simazine although presently classified category 3 by IARC have been shown to be associated with an increased risk of prostate cancer (see text). Technical DDT is a mixture of the isomers p,p′-DDT (85%), o,p′-DDT (15%) and o,o′-DDT (<1%) and technical HCH, a mixture of the isomers α, β, and γ. Chlordanes include trans-chlordane, cis-chlordane, trans-nonachlor, cis-nonachlor, and heptachlor.

[4]. Moreover, it has been clearly shown in several European countries that the rise in prostate cancer incidence started long before the initial use of PSA screening test [2, 32]. Unfortunately, there is no available data comparing the rate of use of PSA screening test per inhabitant in Martinique and metropolitan France. However, the health care system in Martinique is rigorously the same as it is in metropolitan France as far as organization, health expenditure, and training of physicians are concerned [20] and the date of PSA screening technique introduction has been identical in both cases. Consequently, it is unlikely that the significantly different higher level of incidence rates observed in Martinique might be due to a difference in screening. Indeed, if we suppose that during our study observation period, the incidence of prostate cancer observed in Martinique, which is situated far away from metropolitan France, would have been associated with a less frequent use of PSA test, the results would have been exactly the opposite of what we observed, that is, a lower rate of prostate cancer incidence. Inversely, for similar reasons, it would be not meaningful to speculate that a less frequent use of PSA test would account for the lower incidence rate of prostate cancer observed in metropolitan France, since the PSA test has been initially developed in this country.

Similarly, life expectancy at birth of the population in Martinique does not differ from the one in metropolitan France (Table 1), confirming that quality of health care system, socioeconomic status, and lifestyle-related behaviour of people living in Martinique and metropolitan France cannot *per se* account for the observed difference in incidence. Therefore, this led us to look for other parameters which could account for the higher incidence rate of prostate cancer in Martinique as compared to metropolitan France.

As observed in USA, men of African descents when compared to Caucasians have been shown to be associated with an ethnographic genetic factor making them more susceptible to prostate carcinogenesis while they both are living in the same environment [33]. Therefore, the difference in incidence rates between Martinique and metropolitan France could be explained from a genetic perspective by the African origin of Caribbean population [34]. Considering the incidence growth curve in Martinique is constantly at a significantly higher level than it is in metropolitan France, and that after log transformation this growth curve is parallel to that of metropolitan France (see Figures 1 and 2), this strongly suggests that not only a Caribbean African descent-associated genetic susceptibility factor is involved in prostate carcinogenesis in Martinique, as it is the case for American African descents living in the USA [35], but also that this factor remained constant during the one generation observation period (1980–2005). However, the local environment in Martinique and metropolitan France is quite different. As indicated in Table 1, albeit they are genetically close if not equivalent to that of Martinique and living in similar regional areas Caribbean populations appear generally to have much lower prostate cancer incidence rates. This suggests that in addition to the ethnographic genetic factor, a nongenetic factor or rather a strong interaction between genetic and environmental factors may be involved in countries or territories with high rates of prostate cancer incidence. However, values of prostate cancer incidence in Caribbean countries or territories where there is no available specific cancer incidence registry may be underestimated, because uptake of PSA testing might be lower, as it may be the case in USA for black men in comparison to with Caucasians [36]. As discussed above, a difference in PSA screening use between Martinique and metropolitan France is unlikely. Furthermore, as reported in Table 1, Cuba for which a specific cancer incidence registry does exist is associated with a significant lower prostate cancer incidence rate than in the USA despite the fact there is a similar percentage of African descents in both countries. Yet, a similar discrepancy does exist when comparing the prostate cancer incidence rate in Sweden to that in UK, while these countries, which both have similar high level health care systems and excellent specific cancer incidence registries, have a similar percentage of African descents (Table 1). With regards to Martinique and metropolitan France, it would have been instructive to know the incidence rate of prostate cancer in the Caucasian population in Martinique. Unfortunately, such data are not available. As reported by IARC in the Globocan 2008 database, the discrepancy between the incidence rates in Martinique and

Guadeloupe should be noted considering that the population and local environment are seemingly similar if not identical. Therefore, it appears that an environmental factor specific to Martinique could be responsible for the higher elevated prostate cancer incidence rate in this island.

On the basis of epidemiological studies, an increase in prostate cancer incidence in people migrating from low cancer incidence countries to high incidence ones [35, 37, 38] has been observed, suggesting that lifestyle-related and/or environmental factors could be potential risk factors for prostate cancer [39, 40]. However, the carcinogenic role of so-called westernized dietary regimens which mainly consists of a low intake of antioxidants still remains unclear. The association of prostate cancer risk with dietary factors such as high intake of fat, meat, and dairy products has been considered [35, 41], but several epidemiological studies have shown conflicting negative results [35, 42]. On the basis of our analysis of international available data, we found that life expectancy at birth was strongly correlated with dietary energy and fat supply or consumption, whereas we could not find any correlation between prostate cancer incidence and dietary energy and fat supply or consumption. For example, despite the fact that during the period 1988–1990, Cuba, was believed to have one of the highest level of daily calories per person in the Caribbean, as indicated in Table 1, prostate cancer incidence is the lowest, whereas albeit Martinique had the lowest level of daily calories per person in comparison with the ones in UK, Sweden, France, and USA, and for this reason is considered to be associated with a modest diet westernization [43], prostate cancer incidence is the highest. A further argument suggesting a possible role of environmental causes in the growing incidence of prostate cancer is that although UK is associated with a high level of dietary energy and fat supply and consumption similar to that in USA, Sweden, and France, prostate cancer incidence rate is one of the lowest of Western countries, as it is the case for Cuba (Table 1). And this is particularly true for men of African or Caribbean origin living in UK, since for this specific population, prostate cancer incidence rate is 70% less than the corresponding one for African descents living in USA [34]. Moreover, it has been shown in the European prospective investigation into cancer and nutrition (EPIC) study that fruits and vegetables do not protect against prostate cancer [44]. These data therefore strongly support the concept that risk factors other than those related to lifestyle are associated with prostate cancer occurrence, that dietary antioxidants do not play a protective role against prostate cancer, and consequently that mechanisms other than free radicals production are involved in prostate carcinogenesis [30].

Lifetime exposure to endogenous androgens and estrogens has been suggested to be a risk factor for prostate cancer [45, 46], but this endogenous model does not fit in the results of the present study showing a continued increase of cancer incidence since 1985.

We have previously distinguished lifestyle-related risk factors from environmental cancer-causing agents and defined the latter as exogenous physical, chemical, and biological carcinogens or cocarcinogens [2, 4, 47].

As shown in Figures 1 and 2, although significantly differing in levels, the two incidence rate growth curves follow a similar exponential pattern. This may reflect a similar overall effect of different environmental factors, in the framework of gene-environment interactions, whatever these factors could be. In many developed countries including metropolitan France, such factors are unknown. The lack of major industries and associated sources of industrial pollution in Martinique suggests that a factor linked to agriculture may be involved, considering that agriculture is the main economic activity of the island. As indicated in Table 3, several carcinogenic, mutagenic, and/or reprotoxic (CMR) or presumed CMR pesticides including dichloro-diphenyl-trichloroethane (DDT), hexachlorocyclohexane (HCH), chlordanes, aldrin, dieldrin, chlordecone, and simazine have been used in great quantities since 1950 in Martinique for the preventive treatment of banana plantations. We have shown that several of these pesticides used between 1950 and 1970 in Martinique have been detected at considerably high levels in the adipose tissue of all subjects tested [7]. In Martinique, as it is the case for prostate cancer, there is also a recently growing incidence of breast carcinoma [8], and we have proposed that organochlorine pesticides alone or through cocktail effects could cause both prostate and breast cancers by acting through similar common endocrine disruption mechanisms [48]. Many epidemiological studies—but not all—have reported that exposure to organochlorine pesticides is associated with an increased risk of prostate cancer and that among the different pesticides which have been used intensively since 1950 in Martinique, DDT and 1,1-dichloro-2,2′-bis-p-chlorophenyl-ethylene (DDE) [49, 50], Lindane [51], aldrin and dieldrin [49], chlordane [49], heptachlor [49, 51], oxychlordane [52, 53], and the nonorganochlorinated pesticide simazine [53] are associated with a significantly increased risk of prostate cancer and/or are detected at significantly higher levels in prostate cancer patients than in controls. Also, more recently, a case-control study carried out in Guadeloupe has revealed that exposure to chlordecone, an organochlorine pesticide with strong oestrogenic properties used both in Martinique and Guadeloupe, is associated significantly with an increased prostate cancer risk [54]. But this study does not prove that chlordecone, is the cause of the continuous growing incidence of prostate cancer in these two islands. Other factors including the use of other pesticide types may be involved. As suggested in Table 2, except for Sweden, for which factors other than pesticides are probably involved, the amount of pesticides used expressed per inhabitant appears to be more than four times higher in Martinique than what it is in metropolitan France, and there seems to be a statistically significant positive correlation between the incidence rates of prostate cancer and the levels of exposure to pesticides in the different countries analyzed, suggesting that among the environmental factors causally involved in prostate carcinogenesis the intensive use of pesticides could be implicated.

In conclusion, we suggest that the high incidence rate of prostate cancer in Martinique may, in fact, be the result of gene-environment interactions in highly genetically susceptible African descent individuals, that environmental factors

may account for the continued increase of incidence of this cancer, and that among these factors, CMR or presumed CMR organochlorine pesticides may play a role. Further investigations are, however, needed to determine precisely which causative factors are actually specifically involved.

Abbreviations

ASR: Age-standardized rate
CI: Confidence intervals
CMR: Carcinogenic, mutagenic, and/or reprotoxic
DDE: 1,1-dichloro-2,2′-bis-p-chlorophenyl-ethylene
DDT: Dichloro-diphenyl-trichloroethane
DEC: Dietary energy consumption
DES: Dietary energy supply
EPIC: European prospective investigation into cancer and nutrition
FC: Fat consumption
HCH: Hexachlorocyclohexane
IARC: International Agency for Research on Cancer
InVS: French National Sanitary Surveillance Institute
LEB: Life expectancy at birth
PSA: Prostate-specific antigen
REML: Restricted maximum likelihood
SEER: Surveillance, epidemiology, and end results.

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Clinical Study

A Retrospective Study on Pathologic Features and Racial Disparities in Prostate Cancer

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We reviewed more than 3,000 pathology reports on prostate cancer-related surgical specimens and analyzed racial disparities in histological and clinical features at the time of initial biopsy, diagnosis of prostate cancer, and prostatectomy, as well as in characteristics of tumor evolution between African American and Caucasian patients. As compared to Caucasians, African American patients had younger age, higher cancer detection rate, higher Gleason score of prostate cancer, and more bilateral involvement of the prostate. African Americans also had larger prostates, greater volume of tumor, and more positive margins. The diagnosis of HGPIN or ASAP in prostate biopsies and African American race conferred an increased risk of diagnosis of prostate cancer. The interval between prior noncancerous biopsy and the subsequent biopsy with diagnosis of prostate cancer was shorter in men with HGPIN, with ASAP, or of African American race.

1. Introduction

African American race along with age and family history are well-established risk factors for prostate cancer [1]. A better understanding of the racial disparities in prostate cancer between African Americans and Caucasians is crucial to elucidating the pathogenesis of this disease, developing rational diagnostic and screening strategies, and facilitating discovery of new interventions for prevention and treatment of prostate cancer. That African Americans have higher incidence and mortality rates than Caucasians is clear from epidemiological studies using nationwide databases such as the SEER database maintained by the National Cancer Institute [2]. Many studies have demonstrated that there was higher detection rates of prostate cancer in biopsies from African Americans compared to Caucasians [3–6], while other studies suggest that race might not be independently associated with a positive biopsy in men suspected of having prostate cancer [7–9]. It has been commonly accepted that high-grade prostatic intraepithelial neoplasia (HGPIN) is an important histological precursor of prostate cancer since it was precisely characterized by McNeal and Bostwick [10], and atypical small acinar proliferation (ASAP) is a histological finding associated with a high rate of current carcinoma not sampled at the time of biopsy [11]. Both lesions are generally believed to be important predictors for prostate cancer on rebiopsy [12–14]. Racial differences in prevalence of these important histological patterns have been demonstrated in prior studies [4, 15], but the significance of such distinctions and application of this knowledge are not agreed upon. For example, the role of race in developing strategies for rebiopsy in men with HGPIN is controversial [6, 16]. Thus, the influence of these characteristic lesions on the evolution of prostate cancer needs to be further studied.

There are many potential reasons for these discrepancies between studies of racial differences in histological features associated with prostate cancer, including lack of reproducibility in the diagnosis of HGPIN or ASAP [13]. One of the most important limitations in our understanding in this area is that African Americans remain underrepresented in most cancer studies [17–19]. There is a need for additional studies from regions and institutions with populations which include a substantial proportion of African Americans. The population of Mississippi is comprised of a relatively stable

racial/ethnic mix, and most individuals in the state identify themselves as either African American or Caucasian (~98%) with a nearly balanced proportion [20]. Less than 1% of people from Mississippi were reported as more than one race in census data [21]. Importantly, incidence and mortality rates from prostate cancer in Mississippi rank among the nation's highest [22]. The current study will retrospectively analyze the pathology reports and clinical data for African American and Caucasian patients with prostatic diseases from the Mississippi region. We will emphasize the racial disparities in pathological and clinical features at the time of initial biopsy, diagnosis of prostate cancer, and prostatectomy, as well as in the characteristics of tumor evolution.

2. Materials and Methods

2.1. Patient Population, Data Collection, and Categorization. All patients were registered at the University of Mississippi Medical Center (UMMC), a state owned tertiary care hospital between 1989 and 2009. A large majority of the patients were from Mississippi. Records of patients with surgical specimens from the prostate or other sites with metastatic prostate cancer were reviewed for this study. Of 2,403 patients, 1261 (52.48%) were African American, and 1019 (42.41%) were Caucasian, 9 (0.4%) were other races including Asian, Hispanic, and American Indian. The remaining 114 (4.7%) were patients without racial/ethnic information recorded.

Pathology reports for each surgical specimen were reviewed. Patient medical history and laboratory data were obtained from electronic databases at the UMMC. Most of the pathologic diagnoses were made by one of the authors (SB). Cases were categorized as benign, HGPIN, ASAP, primary prostate cancer, and metastatic prostate cancer. Specimens with more than one diagnosis were included in only one group by assigning them to the highest category present in descending order from metastatic prostate cancer, primary prostate cancer, ASAP and HGPIN to benign. Twenty-three surgical specimens were excluded from the study: 6 with benign diagnoses, including 3 adenomas, 1 leiomyoma and 2 papillomas, and 17 with malignant diagnoses, including 1 adenoid basal cell tumor, 1 adenocarcinoma unspecified, 2 sarcomas, 2 squamous cell carcinomas, 1 stromal and epithelial tumor, and 10 transitional cell carcinomas. Racial differences were analyzed only between African American and Caucasian patients due to limited numbers from other racial groups.

2.2. Prostatic Biopsy. Indications for an initial prostatic biopsy included elevation of serum PSA (>4 ng/mL), abnormal digital rectum examination (DRE), and clinical manifestations of urinary outlet obstruction. Repeat biopsies were mostly performed for patients who had previously negative biopsy for prostate cancer in whom there was high clinical suspicion for prostate cancer. Included in this study, approximately 61% biopsies were standard sextant biopsies; the other biopsy cases had a variable number of additional biopsy cores. During the study period, a total of 2,248 prostatic biopsies were performed by multiple urologists. All criteria and procedures and protocols were the same for patients from African American and Caucasian populations.

2.3. Prostatectomy. In this study, a total of 442 prostates were surgically removed. Among these, 361 (81.7%) cases were radical retropubic prostatectomies, and 81 (18.3%) patients underwent cystoprostatectomy. When the entire prostate (or with urinary bladder in cystoprostatectomy) was removed, it was immediately fixed in formalin. The prostate, after the removal of seminal vesicles, was weighed in grams at the time of gross examination. A few prostates were not weighed (mostly attached with diseased urinary bladder) and their weights were estimated by three dimensional measurements with the formula: weight (grams) = length (cm) $\times$ height (cm) $\times$ width (cm) $\times$ 3.14/6 [23]. The entire prostate was sectioned at 3 mm thickness and processed and stained with hematoxylin eosin routinely for pathology study. The percentage of tumor, the proportion of tissue area occupied by tumor in the entire gland, was estimated by visual inspection (mostly by SB). The tumor volume was calculated using the formula: tumor volume (cm^3) = % of tumor $\times$ weight of prostate (grams). The surgical and pathological procedures were exactly the same for patients from African American and Caucasian populations.

2.4. Parameters in the Evolution of Prostate Cancer. In order to compare the differences in the evolution of prostate cancer between African American and Caucasians, the following parameters were set for comparison: (1) detection rate and features of prostate cancer in repeat biopsies, (2) laterality of prostate pathology in initial biopsy, and (3) time interval between two consecutive prostatic biopsies. The time interval for evolution of prostate cancer was calculated from the time of the latest negative biopsy to the time of the earliest positive sampling in patients who were eventually diagnosed as prostate cancer by repeat sampling.

2.5. Statistical Analysis. Chi-square test was used in comparison of rates or percentages; Wilcoxon-Mann-Whitney test was used to compare medians; Student's t-test was used in comparison of means; exact binomial probabilities calculation was used in testing binomial distributions.

3. Results

A total of 3,315 pathology reports from 2,403 patients have been reviewed. Of 3,315 surgical specimens from the prostate or other sites related to prostate tumors, 1480 (44.7%) were diagnosed as benign changes including diagnoses of normal, hyperplasia, and prostatitis; 252 (7.6%) as HGPIN; 90 (2.7%) as ASAP; 1,435 as primary prostate cancer (43.7%); 35 (1.06%) as metastatic prostate cancer.

3.1. Racial Disparities in Detection Rate, Age, PSA Level, and Tumor Grade at the Initial Biopsy. African Americans had 1,230 biopsies including 1,012 initial biopsies and 218 repeat biopsies from 147 patients; Caucasian had 911 biopsies

Table 1: Differences in percentages of diagnoses at the first biopsy between African American and Caucasian.

Diagnosis	African American (n)	Caucasian (n)	P value
Benign (%)	37.2 (372)	48.4 (370)	<0.0001[a]
Age (Year, mean ± SD)	60.9 ± 8.9 (376)	63.5 ± 9.2 (370)	<0.0001
Serum PSA (ng/mL, median)	5.7 (170)	5.5 (146)	>0.05
PIN (%)	9.1 (92)	9.9 (76)	>0.05
Age (Year, mean ± SD)	61 ± 7.7 (92)	62.4 ± 7 (76)	>0.05
Serum PSA (ng/mL, median)	6.7 (73)	5.5 (39)	>0.05
ASAP (%)	3.3 (33)	2.9 (22)	>0.05
Age (Year, mean ± SD)	60.5 ± 9 (33)	62.4 ± 7 (22)	>0.05
Serum PSA (ng/mL, median)	5.1 (21)	5.8 (13)	>0.05
Prostate cancer (%)	50.3 (509)	38.3 (293)	<0.0001[b]
Age (Year, mean ± SD)	63.2 ± 9 (509)	64.7 ± 9.1 (291)	0.027
Serum PSA (ng/mL, median)	11.6 (346)	7 (162)	<0.0001
Gleason's score (n/mean ± SD)	6.9 ± 1.5 (502)	6.3 ± 1.5 (289)	<0.0001

[a]: OR = 0.63, 95% CI: 0.52–0.76. [b]: OR = 1.63, 95% CI: 1.35–1.97.

Table 2: Differences in features at time of diagnosis of Pca between African Americans and Caucasians.

Features	African American (n)	Caucasian (n)	P value
Prostate cancer detection rate (%)	49.2 (620)	40.8 (416)	<0.0001[a]
Age (year, mean±SD)	63.1 ± 9 (620)	64.7 ± 8.8 (414)	0.0081
Gleason score (mean±SD)	6.9 ± 1.6 (611)	6.3 ± 1.6 (410)	<0.0001
Serum PSA (ng/mL, median)	11.1 (404)	7 (213)	<0.0001
Diagnosed by biopsy (%)	88.9 (551)	79.6 (331)	<0.000[b]
First biopsy (%)	82.1 (509)	70.5 (293)	<0.0001[c]
Repeated biopsies (%)	6.8 (42)	9.1 (38)	>0.05
Diagnosed by TURP* (%)	6.5 (40)	9.6 (40)	0.074[d]
Diagnosed by prostatectomy (%)	4.7 (29)	10.8 (45)	<0.0001[e]

*TURP: Transurethral resection of prostate; [a]: OR = 1.4, 95% CI: 1.19–1.66; [b]: OR = 2.1, 95% CI: 1.45–2.89; [c]: OR = 1.93, 95% CI: 1.44–2.58; [d]: OR = 0.65, 95% CI: 0.41–1.02: [e]: OR = 0.41, 95% CI: 0.25–0.65.

including 765 initial biopsies, and 146 repeat biopsies from 121 patients. At the time of the initial biopsy, the age was significantly younger and the PSA level was significantly higher in African American than in Caucasian patients (mean age: 62 versus 63.8, $P < 0.0001$, median PSA: 8 ng/mL versus 5.8 ng/mL, $P < 0.0001$). As shown in Table 1, the detection rate of prostate cancer on initial biopsy was substantially higher in African American patients than in Caucasian patients (50.3% versus 38.3%, $P < 0.0001$), representing a relative risk of 1.31. Conversely, benign diagnoses excluding HGPIN, and ASAP on the initial biopsy were less common in African Americans than Caucasians (37.2% versus 48.4%, $P = 0.001$). There was no significant difference in the detection rate of either HGPIN or ASAP between African Americans and Caucasians. The mean age at the time of initial prostate biopsy was 1 to 2.5 years younger in African American patients regardless of the diagnosis. In patients with diagnoses of benign, HGPIN and ASAP, there was no significant difference in serum PSA level between the two races. The difference in PSA serum levels between patients with a benign diagnosis and patients with a diagnosis of cancer was much more dramatically increased in African American men (5.7 ng/mL versus 11.6 ng/mL, a 103% difference) than in Caucasian patients (5.5 ng/mL versus 7 ng/mL, a 27% difference).

3.2. Racial Disparities in Variables at the Time of Diagnosis of Prostate Cancer. The racial differences in clinical and pathologic variables at the time of diagnosis for prostate cancer are outlined in Table 2. African Americans not only had significantly higher detection rates of prostate cancer (49.2% versus 40.8%, $P < 0.0001$), but they were also younger (63.1 versus 64.7, $P < 0.0081$), with higher Gleason scores (6.9 versus 6.3, $P < 0.0001$), and with higher serum PSA levels (11.1 versus 7, $P < 0.0001$). Most prostate cancers were diagnosed at the time of the initial prostate biopsy in both races. This was especially true in African Americans, of 620 African American patients with prostate cancer, 509 (82.1%) were diagnosed at the initial prostate biopsy, which was significantly higher than the proportion of Caucasian cancer patients diagnosed at the time of the initial biopsy (293 out of 416, 70.5%, $P < 0.0001$).

3.3. Racial Disparities in Pathologic Features in Radical Prostatectomy. Detailed pathologic features of prostatectomy and

Table 3: Differences in clinical and pathological features at prostatectomy between African Americans and Caucasians.

Features	African American (n)	Caucasian (n)	P value
Total radical prostatectomy (%)	18.7 (236)	21.2 (216)	>0.05
Cystoprostatectomy (%)	9.8 (23)	26.9 (58)	<0.0001[a]
Incidental prostate cancer (%)	39.1 (9)	34.5 (20)	>0.05
Prostate cancer in prostatectomy (%)	78.4 (185)	70.4 (152)	>0.05
Age (year, mean ± SD)	58.7 ± 6.8 (185)	61.5 ± 7.4 (152)	0.0005
Gleason score (mean ± SD)	6.63 ± 1.1 (184)	6.58 ± 1.3 (149)	>0.05
Positive surgical margin (%)	33.5 (62)	19.7 (30)	0.0005[b]
Extracapsular extension (%)	18.9 (35)	17.8 (27)	>0.05
Seminal vesicle invasion (%)	9.7 (18)	8.6 (13)	>0.05
Lymph node invasion (%)	3.2 (6)	1.3 (2)	>0.05
Weight of prostate (grams, median)	46 (127)	45 (97)	>0.05
% of prostate gland (median)	15 (114)	6.6 (94)	0.00506
Volume (cm^3, median)	7.4 (114)	3 (93)	0.00185

[a]: OR= 0.31, 95% CI: 0.18–0.52; [b]: OR = 2.05, 95% CI: 1.243–3.38.

initial diagnostic reports were available for 185 African American and 152 Caucasian patients. The racial differences in pathologic features in radical prostatectomy and cystoprostatectomy specimens are summarized in Table 3. Caucasians had a higher proportion of cystoprostatectomy specimens than African American patients (27.2% versus 9.8%, $P < 0.0001$). In cystoprostatectomy specimens, the rate of incidental prostate cancer (primary purpose of surgically removal of the prostate was not for prostate cancer) in cystoprostatectomy was 39.1% in African Americans and 34.5% in Caucasians (no significant difference). It is worth noting that African American patients diagnosed with prostate cancer were almost 3 years younger than Caucasians at prostatectomy (58.7 versus 61.5, $P = 0.0005$). African American patients had a significantly higher rate of positive resection margins (33.5% versus 19.9%, $P = 0.0005$) than Caucasians. Although the median weight of the prostate was almost the same in the two races, African American patients had a significantly higher median percentage of tumors in the gland (15% versus 6.6%, $P = 0.014$) or more than 2 times of tumor volumes (7.4 cm^3 versus 3 cm^3, $P = 0.012$) as compared to Caucasians. The differences in other pathologic features, including Gleason score, were not significant in the prostatectomy specimens between the two races.

3.4. Racial Disparities in Progression and Evolution of Prostate Cancer. In our study cohort, approximately 7–9% of the patients diagnosed with prostate cancer were identified on repeat prostate biopsy procedures (6.8% in African American and 9.1% in Caucasian). The detection rate of prostate cancer at the repeat biopsy varied with the diagnosis in previous biopsies and races. As shown in Figure 1, both HGPIN and ASAP were associated with increased detection rates for prostate cancer in subsequent biopsies. In African Americans, prostate cancer was detected by repeat sampling in 33% patients with ASAP diagnosed in previous biopsies; this rate was significantly higher than that in patients with PIN (14.7%, $P = 0.01$, OR = 2.9, 95% CI: 1.4–6.2) or only benign features (5.8%, $P < 0.0001$, OR = 8.1, 95% CI: 4.2–15.8) diagnosed in previous biopsies. The difference in detection rate of prostate cancer between patients with previous diagnosis of PIN and benign was also significant (14.7% versus 5.8%, $P = 0.001$, OR = 3.0, 95% CI: 1.6–4.8). In Caucasians, prostate cancer was detected by repeat sampling in 20.6% of patients with PIN diagnosed in previous biopsies; this rate was significantly higher than that in patients with ASAP (13.8%, $P = 0.01$, OR = 2.9, 95% CI: 1.4–6.2) or only benign features (5.1%, $P < 0.0001$, OR = 4.8, 95% CI: 2.7–8.7) diagnosed in previous biopsies. There was no statistical difference between the two races in the detection of prostate cancer by repeat sampling from patients with previous diagnoses of ASAP, PIN, and benign although prostate cancer detected by repeat sampling in patients with ASAP diagnosed in previous biopsy in African Americans was 2.4 times higher than that in Caucasians (33.3% versus 13.8%, $P = 0.067$, OR = 3.1, 95% CI: 1–10).

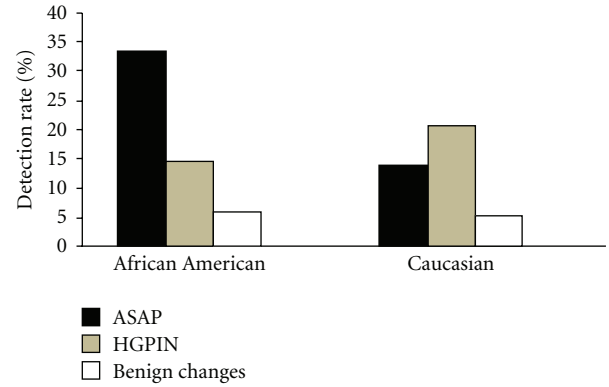

Figure 1: Comparison of prostate cancer detection rate in repeat sampling between African American and Caucasian.

In African American patients in which there was clinical suspicious for prostate cancer, the time interval, which was calculated from the time of noncancer at the previous biopsy to the progression of prostate cancer at the subsequent

Table 4: Differences in bilaterally distribution of HGPIN, ASAP, and prostate cancer diagnosed at the first biopsy between African American and Caucasian.

	African American	Caucasian	*P* value
	n/N	*n/N*	
HGPIN	41/90 (45.6%)	25/75 (33.3%)	0.004[a]
ASAP	7/30 (23.3%)	1/21 (4.8%)	0.119[b]
Prostate cancer	295/479 (61.5%)	97/274 (35.4%)	<0.0001[c]

n = number of bilateral distribution; *N* = total cases with available information on pathology distribution; [a]: Ratio = 2.51, 95% CI: 1.3–4.9; [b]: Odds Ratio = 6.08, 95% CI: 0.6–143.3; [c]: Odds ratio = 2.93, 95% CI: 2.1–4.

biopsy, was 7 months for those with previous diagnosis of HGPIN or ASAP and 9 months for those with previous diagnosis of benign. In Caucasian patients, that time interval was 8 months for those with previous diagnosis of HGPIN or ASAP and 22.5 months for those with previous diagnosis of benign. These data suggest that prostate cancer might progress more rapidly in African Americans with persistently elevated PSA, especially those with previous diagnosis of benign, as compared to Caucasians.

Information regarding laterality of prostate pathology diagnosed at initial biopsy was available for 969 patients, including 165 patients with HGPIN, 51 patients with ASAP, and 753 patients with prostate cancer. African Americans patients had higher percentages of bilateral distribution of all HGPIN, ASAP, and prostate cancer than Caucasians. The differences were significant in HGPIN ($P = 0.004$) and in prostate cancer ($P < 0.0001$). Although African Americans had a higher percentage of bilaterally distributed ASAP than Caucasians (23.3% versus 4.8%) with an odds ratio of 6.08 (Table 4), the difference was not statistically significant. These results suggest that prostate cancer was more advanced in African Americans at the time of initial biopsy than in Caucasians.

In 142 unilaterally distributed HGPIN and ASAP, it was significantly more commonly detected on the left side (88 out of 142, 62% in left half of prostate, with a Z-ratio of +2.77, $P = 0.0054$). This left predominance remained similar in both lesions of HGPIN and ASAP and in both races. The significance of this phenomenon is not determined but may be due to the handedness of the physicians performing the biopsies.

4. Discussion

This retrospective study demonstrates that, in this cohort of African American and Caucasian men undergoing biopsy or resection for prostate cancer, there are significant racial differences in clinical and pathologic parameters. African Americans were younger at the time of initial biopsy and at the time of cancer diagnosis. The detection rate for prostate cancer was nearly 30% higher in African American men undergoing an initial biopsy procedure than for Caucasian men, and the cancers detected on initial biopsy procedure were 70% more likely to be bilateral and with higher Gleason scores in African Americans. Prostate cancers in African Americans had greater volume and occupied a higher percentage of the prostate gland than cancers in Caucasians, and African Americans were more likely to have positive surgical resection margins at prostatectomy than Caucasians. If patients with positive surgical resection margins were accounted into non-organ-confined disease, African Americans had a significantly higher rate of non-organ-confined diseases at the time of prostatecotomy for cancer as compared to Caucasians (non-organ-confined cases was 43.4% in African American 32.9% in Caucasian, $P = 0.044$, data not shown in results). Of course, some positive surgical resection margins might be technically produced by transection of organ-confined tumors.

Cancer detection at the time of the initial prostate biopsy procedure was higher in both races in our study compared to reported rates in the medical literatures [24, 25]. The University of Mississippi Medical Center is the only allopathic medical school in Mississippi and is an important tertiary referral center for medical care. Mississippi, in addition to having a high proportion of African American citizens, is also a relatively poor state with lower per capita income and fewer physicians per capita than other states, which may contribute to lower rates of participation in health screening endeavors, including PSA screening. These factors may contribute to the higher rates of cancer detection on initial biopsy and the higher levels of PSA at initial diagnosis, compared to published data.

The focus of this review was to evaluate histological features of prostate tissue samples including biopsies and resections to identify racial differences and to correlate the differences with clinical factors associated with increased risk and poor prognosis for prostate cancer in African Americans. We were able to identify higher rates of prostate cancer precursors in African Americans and to show that both HGPIN and ASAP are important risk factors for subsequent diagnosis of adenocarcinoma in both races. In fact, the risk of subsequent cancer diagnosis for both HGPIN and ASAP was higher in African American patients than in Caucasian patients. This supports the concept that prostate cancer development in African Americans is pathogenetically similar to tumorigenesis in Caucasian patients and is associated with the same precursor lesions. Although African American patients were younger at the time of initial prostate biopsy and at the time of prostatectomy than Caucasian patients, their tumor volumes were greater, probably accounting for the more frequent positive margins, higher PSA levels, and higher frequency of bilateral cancer detection on biopsies. All of these

findings indicate that significant prostate cancer develops at younger ages in African American men than Caucasians, which could have important implications for the development of evidence-based prostate cancer screening recommendations. In our opinion, it is important to inform the African American men in our communities about the risks of prostate cancer and encourage them to participate in appropriate screening programs. Whether African Americans should begin the screening process at a younger age needs to be further addressed. Health care providers need to be aware of these clinical differences and increased risk factors for African Americans.

Prostate cancer volumes in this review were estimates based on visual evaluation of representative, but thorough sampling and more accurate assessments of cancer volume are available from other studies. In our study, the median tumor volume in African Americans was approximately 2.5 times larger than that in Caucasians (7.4 cm^3 versus 3 cm^3); however, the median weight of the entire prostate gland was almost equal between the races (46 grams for African American, 45 grams for Caucasian). The ratio of prostate cancer volume between two races in this study was similar to that reported by Sanchez-Ortiz et al. [26], in which African Americans had 2.8 times larger prostate cancer volume than Caucasians (2.5 times in our study). However, the mean tumor volumes were much smaller (1.82 cm^3 for African American, 0.72 cm^3 for Caucasian) in their study of patients with nonpalpable T1 prostate cancer. Actually, the prostate cancer volume for Caucasians in our study (3 cm^3) was close to that (3.4 cm^3) reported by Moul et al. [27].

The reasons that African Americans develop prostate cancer at younger ages with higher Gleason scores and greater volumes than Caucasians remain unclear. Certainly, delays in diagnosis could be an important factor in African Americans having greater tumor volumes, but the fact that African Americans in our study were younger at the time of initial biopsy would suggest that biological factors could be responsible for these disparities. The differences between the races in androgen concentration, androgen sensitivity, diet, and cultures could be some of the potential factors of the racial disparities in prostate cancer. Perhaps African Americans have similar pathogenetic mechanisms in development of prostate cancer to Caucasians, but they have a faster growth rate and/or an earlier transformation to clinically significant prostate cancer as evidenced by Powell et al. [28].

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Research Article

Prostate Cancer Severity Associations with Neighborhood Deprivation

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Background. The goal of this paper was to examine neighborhood deprivation and prostate cancer severity. *Methods*. We studied African American and Caucasian prostate cancer cases from the Pennsylvania State Cancer Registry. Census tract-level variables and deprivation scores were examined in relation to diagnosis stage, grade, and tumor aggressiveness. *Results*. We observed associations of low SES with high Gleason score among African Americans residing in neighborhoods with low educational attainment (OR = 1.34, 95% CI = 1.13–1.60), high poverty (OR = 1.39, 95% CI = 1.15–1.67), low car ownership (OR = 1.46, 95% CI = 1.20–1.78), and higher percentage of residents on public assistance (OR = 1.32, 95% = 1.08–1.62). The highest quartile of neighborhood deprivation was also associated with high Gleason score. For both Caucasians and African Americans, the highest quartile of neighborhood deprivation was associated with high Gleason score at diagnosis (OR = 1.34, 95% CI = 1.19–1.52; OR = 1.71, 95% CI = 1.21–2.40, resp.). *Conclusion*. Using a neighborhood deprivation index, we observed associations between high-grade prostate cancer and neighborhood deprivation in Caucasians and African-Americans.

1. Introduction

Prostate cancer is the most prevalent malignant cancer among men in the U.S. 217,730 incident cases were expected in 2010 [1]. The advent of prostatic specific antigen (PSA) testing has driven large increases in diagnoses with dramatic increases observed between 1988 and 1993, coinciding with the advent of widespread PSA testing [2–4]. African Americans have a significantly higher risk of disease than Caucasian men, tend to be diagnosed with more aggressive disease, and suffer the greatest mortality associated with prostate cancer [5]. In spite of its common occurrence and strong racial disparities, modifiable risk factors for prostate cancer have not been confirmed. These disparities are believed to be a result of interactions among genes, health behaviors, and environmental factors.

Economic, physical, and social characteristics of residential neighborhoods may influence health-related behaviors, screening behaviors and health conditions. Disadvantaged neighborhoods are often correlated with higher levels of environmental pollutants, overcrowding, violence, less social cohesion, and less access to services [6]. Of particular importance for diseases such as prostate cancer in which screening practices have had large effects on incidence, low-income neighborhoods often have fewer medical facilities and these facilities are often stressed due to higher burdens of indigent care. The effects of race-based residential segregation may also have a distinct effect on the spatial accessibility of health care facilities [7]. A recent national study showed that in the most segregated counties, a greater proportion of African American residents was associated with a significantly lower volume of outpatient surgery, fewer ambulatory surgery facilities, fewer general surgeons, and a significantly higher volume of emergency medical visits [8].

Only a few studies have investigated the effects of neighborhood economic and social conditions on prostate cancer

incidence and aggressiveness at diagnosis. However the extant data suggest that higher socioeconomic status measured at the individual or neighborhood level predicts a higher risk of prostate cancer diagnosis and a lower risk of late-stage disease at diagnosis. The National Program of Cancer Registries Patterns of Care Study found that higher average neighborhood educational attainment and income measured at the Census Tract level is associated with lower-stage prostate cancer at diagnosis [9]. Recent analyses of SEER-Medicare data show that higher zip code level median household income is protective against advanced stage disease at diagnosis [10].

Although socioeconomic and ethnic differences in prostate cancer outcomes persist, no studies of neighborhood level factors have reported on prostate cancer severity as an outcome stratified by race. Additionally, prior studies have tended to focus on single variable indicators of socioeconomic status, for instance percent poverty, which do not necessarily reflect all of the dimensions of socioeconomic stratification across neighborhoods. The aims of this study were: (1) to determine if census tract level SES factors are differentially associated with indicators of prostate cancer severity by race and (2) to determine whether a more comprehensive measure of neighborhood SES more strongly predicted prostate cancer severity than single variable indicators of economic stratification.

2. Materials and Methods

2.1. Study Participants. Anonymized data from the Pennsylvania Department of Health was provided on prostate cancer patients diagnosed in the Commonwealth of Pennsylvania from 1995 to 2007. In the present analysis, we focused on a sample who resided in Southeastern Pennsylvania, the primary service area of patients at the University of Pennsylvania and representative of the Philadelphia metropolitan area. The geocoded subset of patients focused on Philadelphia county and the surrounding 4 counties (Bucks, Delaware, Montgomery, and Chester). This sample identifies a targeted region with a defined population base representing a variety of sociodemographic conditions of interest to the present analysis. Residential addresses of prostate cancer patients in the Pennsylvania cancer registry were cleaned by trained research staff and geocoded with Arc GIS. A total of 5,136 African American and 16,672 Caucasian men were geocoded from this Philadelphia 5-county region.

2.2. Neighborhood Variables. Census data describing the sociodemographic characteristics of the census tracts for the five counties were downloaded from the Census Bureau web site (http://www.census.gov) from 2000 Census Summary File 3. Downloaded data were census tract characteristics of interest for this study. Variables extracted from this database included household income, adult high school educational attainment, percent poverty, percent of female-headed households with dependent children, percent of households with no car, percent of households on public assistance, percent of unemployed adults, percent vacant housing units, percent of homes with more than 1 occupant per room, home value, percent of non-Hispanic Black residents, percent of males in management positions, percent of females in management positions, percent of males in professional occupations, percent of females in professional occupations, percent of rented units, percent of males not in the labor force, percent of total population 65 years and over, percent of residents who did not move since 1995, and percent of renters or owners paying more than 50% of income for home.

We also calculated a deprivation index based on one originally developed and tested by Messer et al. on several geographic regions in the U S [11]. The index uses a principal components analysis (PCA) approach. The deprivation index was used to facilitate the comparison of neighborhood deprivation and health across geographic areas. Twenty census variables described and selected by Messer et al. were included in our PCA [11]. They characterized SES and demographic domains associated with health outcomes in the literature. The variables that loaded in the top 20 percentile (explaining the greatest amount of variance) were retained for inclusion in the deprivation index. These 5 variables were (1) percent of households with income < \$30,000/year, (2) percent poverty, (3) percent of households on public assistance, (4) percent of female head of household with dependent children, and (5) percent of households with no car. A final PCA was run with the 5 retained variables to determine the weight of each variable's contribution to the deprivation score for each census tract in the study area. The weighted deprivation score standardized by SAS to have a mean of 0 and standard deviation of 1 ranged from −1.07 (low deprivation) to +4.02 (high deprivation). Quartiles of continuous neighborhood deprivation were then created.

2.3. Outcome Variables. Our primary outcome variables were indicators of prostate cancer severity that are associated with differences in long-term survival [12]. These variables include tumor stage, with low stage defined as stages 1 and 2 (localized disease), and high-stage is defined as stages 3 and 4 (nonlocalized); tumor grade, with low grade is defined as tumor Gleason score of 6 or below and high-grade is defined as a tumor score of 7 or greater; and tumor aggressiveness, defined as a combined high tumor stage (stage 3 or 4) and high tumor grade (grade 7+) compared to those with other combinations of these variables.

2.4. Statistical Analyses. t-tests were used to compare age means for the groups. χ^2 (frequency) tables were evaluated using Pearson chi-square tests to determine significant differences by race for categorical patient-level and neighborhood-level variables. Generalized estimating models (GEE) using a logit link function, binomial distributions, and robust standard error estimation were used to estimate odds ratios (OR) for associations between neighborhood socioeconomic measures and prostate outcomes accounting for the clustering of multiple patients within census tracts [13]. Two-sided P-values <0.05 were considered significant.

Stratifying the data by race (African American or Caucasian), frequency tables and GEE models were used to determine which neighborhood variables are associated with prostate cancer outcomes. Multicollinearity is an issue when modeling neighborhood variables, so we examined each neighborhood variable in separate models [14]. We also created GEE models to examine the quartiles of the deprivation index in relation to outcome variables. The first quartile, representing lowest neighborhood deprivation, was the reference group. Additional unstratified analyses (adjusting for African American race compared to Caucasian) were conducted to examine whether racial differences are attenuated when census tract-level variables are added to the models. We adjusted for age group <60 or ≥60 and year of diagnosis (modeled as a continuous variable) in all GEE models.

3. Results

3.1. Sample Characteristics. Table 1 presents demographic characteristics of prostate cancer patients by race. There were significant ethnic differences for all patient-level variables ($P < 0.001$). Compared to Caucasians, African Americans were younger (66 versus 68 years), less likely to be married (57% versus 77%), and more likely to have unfavorable prostate cancer characteristics (high-stage, 15% versus 12%, and high Gleason Score, 28% versus 22%).

3.2. Neighborhood SES Characteristics. Table 1 also presents SES characteristics of the patients' residential census tracts. There were significant ethnic differences for all neighborhood-level variables ($P < 0.001$). Compared to Caucasians patients (38-39%), African Americans (86–89%) were more likely to live in low-SES neighborhoods, characterized by below-sample median income and education. The neighborhoods of African American cases were also more likely to have higher than median percentages of poverty, single female head of households, no car ownership, and households on public assistance.

Table 2 presents neighborhood SES indicators in association with prostate cancer severity outcomes. There were no associations of neighborhood SES with aggressive (high-stage and high-grade) tumor in this subset of cases. However, the prevalence of high-stage prostate cancer was lower in Caucasian men living in neighborhoods with high percentage of residents on public assistance (OR = 0.89, 95% CI = 0.80−0.99). No other associations with stage at diagnosis were observed.

The strongest associations between Gleason score and neighborhood SES were observed for African Americans. African Americans residing in neighborhoods with high poverty (OR = 1.39, 95% CI = 1.15−1.67), low income (OR = 1.26, 95% CI = 1.05−1.51), low educational attainment (OR = 1.34, 95% CI = 1.13−1.60), more households with no car (OR = 1.46, 95% CI = 1.20−1.78), and higher percentage of residents on public assistance (OR = 1.32, 95% CI = 1.08–1.62) had a higher Gleason score at diagnosis. Except for ≥ median percent of households with no car (OR = 1.09, 95% CI = 1.01−1.19), there were no associations of these individual neighborhood SES indicators and Gleason score among Caucasians.

3.3. Neighborhood Deprivation. Tumor aggressiveness was associated with the highest level of neighborhood deprivation in Caucasian patients only (OR = 1.27, 95% CI = 1.01−1.59). The overall P-value for neighborhood deprivation for this outcome was not significant ($P = 0.055$). For both Caucasians and African Americans, the highest quartile of neighborhood deprivation was associated with high Gleason score at diagnosis (OR = 1.34, 95% CI = 1.19−1.52; OR = 1.71, 95% CI = 1.21−2.40, resp.; Table 2). The overall P-value for neighborhood deprivation for both groups was <0.001. Trend tests were significant only for Gleason score for both Caucasian ($P \leq 0.001$) and African American patients ($P = 0.002$).

3.4. Race Effects. By conducting an unstratified analysis, we observed that African American race was significantly associated with tumor aggressiveness (OR = 1.31, $P < 0.001$), high-stage (OR = 1.27, $P < 0.001$), and high Gleason score (OR = 1.37, $P < 0.001$) at diagnosis (Table 3). The association between race and prostate cancer severity was only slightly attenuated or remained unchanged when neighborhood SES variables were included in the model. The addition of census tract variables, including the deprivation index, to the models did not change the significance level of race ($P = 0.001$) except in the model including neighborhood deprivation in association with tumor aggressiveness. In this model, the odds of patients with aggressive disease being African American was 1.20 but still significant ($P = 0.020$). The interaction between race and the neighborhood deprivation index was not statistically significant for any of the outcomes ($P = 0.170$ for aggressiveness, $P = 0.622$ for stage, and $P = 0.416$ for Gleason). Trend tests showed that increasing deprivation was associated with increased odds of high Gleason score in the combined sample ($P < 0.001$). No significant trends were observed for the other two outcomes.

4. Discussion

Our first study aim was to examine if neighborhood SES was differentially associated with prostate cancer severity comparing African American and Caucasian prostate cancer patients. We found that there were differences in observed associations for both groups. There were associations with low neighborhood SES and outcomes involving the Gleason score, primarily among African American cases. Most of these neighborhood variables measure similar SES parameters, so observed associations are expected for multiple variables and in the same direction. Although African Americans are at high risk for advanced prostate cancer, it is interesting that this particular outcome and not stage is so consistently associated with low neighborhood SES only in African Americans. This is the first report that the authors are aware of showing this difference by race and suggests that tumor grade in African Americans may be particularly prone to neighborhood influences.

Table 1: Demographics of southeastern Pennsylvania cancer registry prostate cancer patients (1995–2007).

	Caucasian ($N = 16672$)	African American ($N = 5136$)	P value
Patient-level variables			
Age at diagnosis, mean (SD)	67.6 (8.94)	66.0 (9.21)	<.001
Married	12826 (77%)	2931 (57%)	<.001
High stage (III/IV)	2040 (12%)	785 (15%)	<.001
Gleason score (7+)	3697 (22%)	1441 (28%)	<.001
Aggressive tumor	1053 (6%)	423 (8%)	<.001
Neighborhood-level variables			
≥ Median % neighborhood poverty	6381 (38%)	4582 (89%)	<.001
≥ Median % household income < $30,000	6401 (38%)	4482 (87%)	<.001
< Median % high school education	6478 (39%)	4412 (86%)	<.001
≥ Median % female head of household with dependent child(ren)	6307 (38%)	4607 (90%)	<.001
≥ Median % households with no car	6341 (38%)	4595 (89%)	<.001
≥ Median % public assistance	6319 (38%)	4583 (89%)	<.001

Table 2: Stratified analysis—associations of neighborhood SES characteristics with indicators of prostate cancer severity (GEE) adjusted for age and diagnosis year.

Effect	Tumor aggressiveness		High stage		High Gleason	
	Caucasian OR (95% CI)	African American OR (95% CI)	Caucasian OR (95% CI)	African American OR (95% CI)	Caucasian OR (95% CI)	African American OR (95% CI)
≥ Median % neighborhood poverty	0.98 (0.86, 1.12)	1.08 (0.79, 1.48)	0.92 (0.83, 1.03)	0.97 (0.78, 1.22)	1.05 (0.97, 1.14)	1.39*** (1.15, 1.67)
≥ Median % household income < $30,000	1.06 (0.93, 1.22)	0.98 (0.74, 1.29)	1.01 (0.91, 1.12)	0.99 (0.80, 1.23)	1.08 (0.99, 1.17)	1.26* (1.05, 1.51)
< Median % high school education	1.12 (0.99, 1.28)	1.14 (0.87, 1.48)	1.01 (0.91, 1.13)	1.02 (0.84, 1.24)	1.07 (0.98, 1.15)	1.34** (1.13, 1.60)
≥ Median % female head of household with dependent child(ren)	1.03 (0.90, 1.18)	0.97 (0.71, 1.32)	0.94 (0.84, 1.04)	1.00 (0.79, 1.27)	1.07 (0.99, 1.16)	1.18 (0.97, 1.44)
≥ Median % households with no car	1.02 (0.89, 1.16)	0.99 (0.74, 1.33)	0.94 (0.84, 1.04)	0.91 (0.73, 1.14)	1.09* (1.01, 1.19)	1.46*** (1.20, 1.78)
≥ Median % public assistance	0.96 (0.84, 1.10)	1.02 (0.75, 1.40)	0.89* (0.80, 0.99)	0.95 (0.76, 1.19)	1.04 (0.96, 1.13)	1.32** (1.08, 1.62)
Deprivation quartile 2 versus 1	1.04 (0.89, 1.21)	1.84 (0.98, 3.46)	0.98 (0.87, 1.11)	1.28 (0.82, 2.01)	1.05 (0.96, 1.15)	1.32 (0.89, 1.95)
Deprivation quartile 3 versus 1	0.91 (0.76, 1.08)	1.45 (0.81, 2.58)	0.90 (0.78, 1.04)	0.97 (0.65, 1.45)	1.01 (0.90, 1.13)	1.36 (0.96, 1.94)
Deprivation quartile 4 versus 1	1.27* (1.01, 1.59)	1.62 (0.93, 2.81)	0.98 (0.82, 1.18)	1.13 (0.77, 1.64)	1.34*** (1.19, 1.52)	1.71** (1.21, 2.40)
Deprivation quartile, P value	$P = 0.055$	$P = 0.227$	$P = 0.512$	$P = 0.239$	$P < .001$***	$P < .001$***

*< .05, **< .01, ***< .001.

The Gleason score may be less affected by screening practices than stage at diagnosis, and therefore may be more closely tied to biological mechanisms of prostate cancer progression. Although speculative, these mechanisms may be genetic or tied to other risk factors that are disproportionately prevalent among African Americans. Obesity is one factor that is more common in African Americans and is associated with a biologically more aggressive form of prostate cancer [15]. Obesity varies by SES factors and, therefore, may be even more relevant in the discussion of prostate cancer disparities. As African Americans are much more likely than Caucasians to live in disadvantaged areas

Table 3: Unstratified analysis—associations of neighborhood SES characteristics with indicators of prostate cancer severity (GEE) adjusted for age, race, and diagnosis year.

Effect	Tumor aggressiveness		High stage		High Gleason	
	OR (CI)	*P* value	OR (CI)	*P*-value	OR (CI)	*P*-value
African American race/ethnicity	1.31 (1.16, 1.47)	<.001	1.27 (1.17, 1.39)	<.001	1.37 (1.27, 1.47)	<.001
≥ Median % neighborhood poverty	0.99 (0.87, 1.12)	0.853	0.93 (0.84, 1.02)	0.126	1.09 (1.01, 1.17)	0.028
African American race/ethnicity	1.32 (1.15, 1.50)	<.001	1.32 (1.20, 1.46)	<.001	1.31 (1.21, 1.42)	<.001
≥ Median % household income < $30,000	1.05 (0.93, 1.19)	0.446	1.00 (0.91, 1.10)	0.998	1.10 (1.02, 1.19)	0.014
African American race/ethnicity	1.28 (1.12, 1.46)	<.001	1.27 (1.15, 1.41)	<.001	1.31 (1.20, 1.42)	<.001
< Median % high school education	1.12 (1.00, 1.27)	0.054	1.01 (0.92, 1.11)	0.802	1.10 (1.02, 1.19)	0.010
African American race/ethnicity	1.24 (1.09, 1.41)	<.001	1.27 (1.15, 1.39)	<.001	1.31 (1.21, 1.42)	<.001
≥ Median % female head of household with dependent child(ren)	1.02 (0.90, 1.16)	0.727	0.94 (0.85, 1.04)	0.217	1.09 (1.01, 1.17)	0.030
African American race/ethnicity	1.29 (1.13, 1.48)	<.001	1.31 (1.19, 1.45)	<.001	1.31 (1.21, 1.42)	<.001
≥ Median % households with no car	1.01 (0.90, 1.14)	0.845	0.93 (0.85, 1.03)	0.161	1.13 (1.05, 1.22)	0.001
African American race/ethnicity	1.30 (1.14, 1.48)	<.001	1.32 (1.19, 1.45)	<.001	1.28 (1.18, 1.40)	<.001
≥ Median % public assistance	0.97 (0.85, 1.09)	0.576	0.89 (0.81, 0.99)	0.026	1.08 (1.00, 1.16)	0.063
African American race/ethnicity	1.33 (1.17, 1.52)	<.001	1.34 (1.22, 1.49)	<.001	1.32 (1.21, 1.43)	<.001
Deprivation quartile		0.064		0.245		<.001
Deprivation quartile 2 versus 1	1.07 (0.92, 1.24)	0.390	0.99 (0.88, 1.12)	0.882	1.06 (0.98, 1.16)	0.165
Deprivation quartile 3 versus 1	0.94 (0.80, 1.11)	0.470	0.89 (0.78, 1.02)	0.083	1.03 (0.93, 1.15)	0.543
Deprivation quartile 4 versus 1	1.19 (0.99, 1.43)	0.068	0.99 (0.86, 1.14)	0.927	1.36 (1.22, 1.51)	<.001
African American race/ethnicity	1.20 (1.03, 1.39)	0.020	1.27 (1.14, 1.42)	<.001	1.16 (1.06, 1.26)	<.001

*<.05, **<.01, ***<.001.

[16], the possibility of an interaction between patient-level variables and neighborhood-level SES is possible. We were not able to test this hypothesis with the data available in this dataset.

Emerging evidence also indicates that inflammation is a probable pathway for prostate cancer progression [17]. Increased environmental stress is one pathway through which many primary neighborhood factors, such as SES, are believed to exert their effects on the body. It is still unclear what the specific ingredients of a stressful environment that could promote inflammation processes might be. However, the health-modulating effects of chronic stress have been identified as potential pathways that increase risk of disease and may be connected to general SES [18]. Psychosocial stress associated with poverty may increase the risk of many illnesses [19]. In anticipation of an impending challenge, stress that may have been acute (adaptive for our bodies) becomes chronic (pathogenic for our bodies). A prolonged

stress response ultimately results in suppressed immunity and impairs disease defenses. Stress can affect reproductive hormones and immune responses. Cellular and molecular events that promote cancer growth also are affected by stress, and DNA repair mechanisms may be impaired because of stress and cancer defense mechanisms may be disrupted. Stress may influence the expression of viral oncogenes and the replication of tumorigenic viruses. It may also promote tumor growth by facilitating the development of blood supply to the tumor [19].

Differential exposure to stressors may explain a portion of health disparities that we observe by both race and neighborhood SES. Residential neighborhood factors may capture structural and social context that influence overall health and related behavior. Neighborhood deprivation, deterioration, urbanization, poverty, education, segregation, social disorder, and income have been correlated with disease rates and health outcomes [20–28].

We also observed a single inverse association of neighborhood public assistance on stage at diagnosis in Caucasian patients. This finding was unexpected, as it is the only significant, protective relationship observed in these analyses. This neighborhood variable has not been studied in the context of prostate cancer staging or screening. Patient-level data suggests that subsets of patients on Medicaid are at increased risk for late prostate cancer diagnosis [29]. Therefore, it is not clear why our Caucasian subset would be at lower risk for advanced disease if they reside in lower SES neighborhoods.

Income and education are commonly used in the US as measure of patient- and neighborhood-level SES. Both income and educational attainment have been shown to affect risk for cancer diagnosis. A study using the New Jersey Cancer Registry observed clusters of prostate cancer incidence to be associated with geographic areas with higher percentages of foreign-born persons, higher poverty, and lower education [30]. According to SEER data, higher educational attainment has been associated with greater risk of prostate and breast cancers alike. Compared to college-educated men, men with less than a college education were 0.79 as likely to be diagnosed with prostate cancer. Low-income men (family income $<$ \$25,000) were also at lower risk for prostate cancer compared to men with a family income of \$50,000+ [31]. Prostate screening (and therefore prostate incidence) has been shown to be more common in men with higher education, white collar jobs, access to good healthcare, urban residences, and higher household income [32]. A similar positive association between neighborhood SES and breast cancer screening behavior has been observed, even after adjusting for distance to screening facility, urban-rural status, and type of screening facility [33]. Both zip code community SES and zip code urbanicity are positively associated with breast cancer incidence, even after adjusting for individual education [27].

Although, in general, high SES may be associated with prostate cancer incidence/diagnosis, low-SES is associated with more severe disease at diagnosis, suggesting more likely progression and increased risk of cancer-related mortality. Associations between lower neighborhood SES and advanced stage or grade at diagnosis have been observed previously. Lower income has been associated with late-stage prostate cancer diagnosis in the SEER dataset ($P = 0.002$) [31]. Klassen et al. found that subsets of Caucasian men living in high-income areas were at particular low-risk for aggressive prostate tumors [34]. A prostate cancer study in Australia showed that three-year survival was poorer and use of radical prostatectomy was less in men from socioeconomically and geographically disadvantaged backgrounds [35]. Results from the ARIC Study showed that rates of all-cause death, cardiovascular death, and cancer death were greater for men and women living in the lowest income bracket compared to those in the highest [22]. A multilevel study using Florida state data coupled with medical records demonstrated that in addition to individual factors such as Black race, single marital status, current and former smoking status, and older age, advanced prostate cancer was significantly associated with living in census tracts with a low median income and lower percent of residents with a college education [36]. Our study also showed that African American race remained significant even after including neighborhood SES factors in multivariable analysis.

In addition to single variable associations, neighborhood indices representing socioeconomic disadvantage have been associated with various health outcomes [11]. In our study, we found that Caucasians and African Americans in more deprived neighborhoods were more likely to be diagnosed with high-grade prostate cancer. Consistency of these findings with regard to outcomes involving tumor grade may suggest that the deprivation index captures underlying factors of neighborhood SES that together contribute to advanced prostate cancer risk across ethnic groups. Highest levels of neighborhood deprivation were significantly associated with tumor grade in both ethnic groups. To date, few studies have used a deprivation index to examine prostate cancer severity and/or outcomes. One in the UK found that patients from more deprived neighborhoods were more likely than men from less deprived areas to be diagnosed with late stage (stage III or IV) prostate cancer. As in our study, more deprived patients were older. In multivariable analysis, increased deprivation was significantly associated with lower odds of radiation therapy (OR = 0.92, CI = 0.90−0.94) and surgery (OR = 0.90, 95% CI = 0.87−0.94) [37]. A study of the California Cancer Registry used a composite SES score to evaluate treatment outcomes in prostate cancer patients. Men from low-SES areas that were treated by surgery or radiation had increased odds of cancer-specific death. Men from lower SES areas were also half as likely to undergo radical prostatectomy for low-risk disease. Adjusting for race made these findings even more profound. Together, these results may suggest the need for improved screening and treatment in men from low-SES communities [38].

4.1. Study Limitations and Strengths. The limitations of our study include the fact that the cut-points between more and less advantaged neighborhoods are arbitrary and dependent upon our sample characteristics. However, using the deprivation index to examine neighborhood SES will make this study more comparable to future studies that use similar methods. In addition, our study investigated only census

tract-level SES variables, ignoring other contextual characteristics that vary by family, social networks, workplace, and other levels of socially/physically bounded measures of community/geography. We may also be limited by the "intersection of racial and SES segregation," in which there are relatively few African Americans in the least deprived areas and few Caucasians in the most deprived areas [11]. However, among study areas in the study by Messer et al., Philadelphia showed the largest range in deprivation scores [11]. Therefore, studying the Greater Philadelphia area may have provided an opportunity to observe the effects of neighborhood deprivation better than we could have in other urban populations.

Another limitation of this study is that we were unable to determine the length of time at residency and if there are modifying effects that result from duration of exposure [39]. We do not yet know when neighborhood factors are most likely to contribute to cancer outcomes (during childhood or adolescence, during the period before clinical disease onset or after treatment). We also do not know much about the period of time that is required for a particular neighborhood exposure or set of exposures to affect the biology and progression/recurrence of disease in an individual with prostate cancer [40]. Factors like neighborhood SES can be measured at various time points during the lifespan. The relative time frame depends on presumed exposures, causal pathways, and associated etiologic periods [41]. Thus, we have decided to begin our investigation at the point of prostate cancer diagnosis. This allows us to be consistent across all patients. It also provides a sensible timeframe that may be closely linked to the lifestyle and environmental factors that are most likely to influence prostate cancer progression and outcomes. We were unable to evaluate other patient-level variables related to lifestyle and treatment because we were limited by the data collected by the PA Department of Health for these analyses.

A particular strength of this study is the use of a standardized deprivation scoring system. The use of different and multiple definitions of variables used in previous prostate cancer studies made it difficult to assess the evidence for associations systematically. However, the fact that we find similar associations with prostate cancer when multiple definitions of neighborhood SES are used suggests the validity of these findings across studies and populations. Composite variables are also less likely to be significantly influenced by changes in single contributing variables over time. In addition, making conclusions based on one neighborhood SES factor without considering the status of other related contextual variables may lead to inappropriate conclusions [11]. We were also able to determine relationships between neighborhood deprivation and prostate cancer severity by race. Other studies of neighborhood deprivation and prostate cancer severity have not had the diversity to examine patterns of association stratified by race [42] or have only adjusted for ethnicity in multivariable analyses [38]. Evidence of an association between the environment and prostate cancer outcomes can increase our knowledge about risk factors for prostate cancer and stimulate new ideas about prevention strategies. This research also may identify segments of the population that may benefit from targeting interventions. Because prostate cancer is so common in the general population, even if only a small increased risk of disease is associated with it, the potential for decreasing the overall morbidity and mortality attributable to neighborhood deprivation may be significant.

5. Conclusions

The goal of this study was to examine the relationship between neighborhood SES or deprivation and prostate cancer severity in a diverse population of patients representing the general population of Southeastern Pennsylvania. We found significant differences in neighborhood SES by race. We also observed differences in prostate cancer severity by neighborhood SES and higher degree of neighborhood deprivation. The associations were strongest and most consistent for African Americans.

The science of studying health disparities and neighborhood characteristics (from appropriate methods and models to proper outcome measures and results interpretation) is still young. Future analyses examining this deprivation index in other ethnic groups and in multilevel models may help to determine the effect of neighborhood SES on prostate cancer outcomes. Understanding which neighborhood-level variables best predict poor health outcomes in different environmental settings may aid all researchers in unraveling the complexities of prostate cancer disparities in America.

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Research Article

The Metabolic Syndrome and Biochemical Recurrence following Radical Prostatectomy

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Metabolic syndrome refers to a set of conditions that increases the risk of cardiovascular disease and has been associated with an increased risk of prostate cancer, particularly among African American men. This study aimed to estimate the association of metabolic syndrome with biochemical recurrence (BCR) in a racially diverse population. Among 383 radical prostatectomy patients, 67 patients had documented biochemical recurrence. Hypertension was significantly, positively associated with the rate of BCR (hazard ratio (HR) = 2.1; 95% CI = 1.1, 3.8). There were distinct racial differences in the prevalence of individual metabolic syndrome components; however, the observed associations with BCR did not differ appreciably by race. We conclude that hypertension may contribute to a poorer prognosis in surgically treated prostate cancer patients. Our findings suggest that targeting components of the metabolic syndrome which are potentially modifiable through lifestyle interventions may be a viable strategy to reduce risk of BCR in prostate cancer.

1. Introduction

Prostate cancer is the most common invasive cancer diagnosed in men and the second leading cause of cancer death [1]. Of the men who undergo radical prostatectomy for localized prostate cancer, between 17% and 53% will experience biochemical recurrence (BCR) in the ten years following surgery [2, 3]. Traditional predictors of recurrence following radical prostatectomy include preoperative prostate-specific antigen (PSA) levels, tumor stage, Gleason's score, and surgical margin status [3, 4]. While these predictors are often used for determining BCR-free survival probabilities following radical prostatectomy [4], they are nonmodifiable characteristics of disease and as such do not provide patients with options to positively influence their disease course. Given the high level of motivation of most patients in the early postsurgery follow-up period, modifiable targets for intervention that can increase or permanently delay the time to BCR would be beneficial [5].

Metabolic syndrome, which is a risk factor for cardiovascular disease, refers to a clustering of conditions that include hypertension, diabetes, abdominal obesity, hypertriglyceridemia, and low high-density lipoprotein (HDL) cholesterol, with insulin resistance as the underlying hallmark feature [6]. The metabolic syndrome profile differs depending upon race, with Caucasians disproportionately affected with dyslipidemia and African Americans more likely to be diagnosed with hypertension and diabetes [7, 8].

Several studies indicate that the metabolic syndrome is associated with an increased risk of prostate cancer [9–12]. Recent findings from our own group suggest in fact that race modifies the association; metabolic syndrome was positively associated with prostate cancer risk among African American men, but not among Caucasian men [13].

Metabolic syndrome has an appeal as a predictor of BCR as its components can be treated and thereby provide clinicians with a strategy for tertiary prevention. To our knowledge, the association between metabolic syndrome and prostate cancer recurrence has never been systematically investigated. Therefore, the aims of this study were to estimate the effects of metabolic syndrome and its individual components on prostate cancer BCR and to determine if racial differences exist with regard to the associations of interest.

2. Materials and Methods

2.1. Study Population and Data Collection. The data for this investigation were collected as part of a prostate cancer case-control study conducted at the Henry Ford Health System (HFHS) in Detroit, Michigan, USA. HFHS provides care to a racially diverse population in the Detroit Metropolitan area [14]. Eligibility criteria for participation in the current study included (1) ≤75 years of age at time of diagnosis, (2) use of HFHS for the patient's primary medical care in the 5 years prior to diagnosis, (3) residence within the study area at time of recruitment, (4) no serious medical problems that would prohibit participation, and (5) radical prostatectomy as the patient's primary treatment. Cases were diagnosed with primary adenocarcinoma of the prostate between January 1, 1999 and December 31, 2004. The diagnosis was histopathologically confirmed by the HFHS Department of Pathology. Three hundred-ninety-six (396) prostate cancer cases were considered eligible for the current investigation based on the aforementioned criteria, with African American men comprising approximately 40% of the study population. All participants completed an interviewer-administered questionnaire. The questionnaire included information on sociodemographic characteristics, family history of prostate cancer, health behaviors including smoking history and physical activity, occupation, diet, height and weight. Data extracted from medical records included hypertension, diabetes and lipid profiles, PSA screening history, pretreatment PSA levels, clinical and pathological TNM stage, and biopsy and surgical Gleason's scores. Informed consent was gathered from all participants, and the HFHS Institutional Review Board approved all protocols.

2.2. Metabolic Syndrome Definition. Metabolic syndrome was defined using criteria established by the National Cholesterol Education Program Expert Panel on the Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III (ATP)) [15]. The ATP III definition requires any three of the following five components: (1) hypertension (≥130/85 mmHg), (2) high fasting blood glucose (≥110 mg/dL), (3) abdominal obesity (waist circumference >102 cm in men), (4) low high-density lipoprotein (HDL) cholesterol (<40 mg/dL), and (5) hypertriglyceridemia (≥150 mg/dL). In order to accommodate the available study data, specific ATP III criteria were modified. A body mass index (BMI) of greater than 30 kg/m^2 was used as the criterion for abdominal obesity as measures of waist circumference were unavailable. BMI was calculated using self-reported height and weight at time of enrollment. A history of hypertension and/or diabetes prior to their prostate cancer diagnosis was abstracted from the medical record and recorded as present or not present.

2.3. Biochemical Recurrence Definition. Biochemical recurrence (BCR) was defined as two consecutive rising detectable PSA concentrations of >0.2 ng/mL [16]. Our criteria for determining the start of follow-up for identifying men at risk of BCR required that PSA levels reach a nadir ≤0.2 ng/mL after surgery. PSA levels are typically expected to drop to near undetectable levels within the four weeks following radical prostatectomy [17]. To account for the variation in the timing of PSA testing, only those subjects who reached ≤0.2 ng/mL within 6 weeks were included in this analysis. Thirteen subjects were excluded either because they did not reach a PSA nadir within 6 weeks, suggesting some residual disease or lack of PSA follow-up data, making it difficult to determine when nadir was established.

2.4. Statistical Methods. All statistical analyses were performed using Statistical Analysis Systems software, version 9.2 (Cary, NC, USA). Study population's demographic and clinical characteristics were described with appropriate frequency measures. Patient characteristics included age at the time of diagnosis, race, and smoking history. Clinical characteristics included preoperative PSA level, clinical stage (local, regional, distant), tumor grade, and surgical margin status. The distribution of metabolic syndrome components were examined in the total population and stratified by race. Differences in the prevalence of metabolic syndrome components between the races were evaluated with chi-square tests.

Crude and adjusted hazard ratios were estimated using Cox regression. Time to recurrence was modeled as a function of (1) each individual component adjusted for all other components and (2) metabolic syndrome (any 3 of 5 features). Multiple models were fit, adjusting for different combinations of patient and clinical characteristics treated as potential confounders. Age at diagnosis was modeled as a continuous variable. All other covariates were included in models as dichotomous variables. Categorization of these covariates was as follows: a pre-operative PSA level of >10 ng/mL was considered high; a Gleason score 7 (4 + 3) or greater was designated high grade; regional and distant stage designations (as determined from clinical TNM and pathological staging) were categorized as high stage. Models were further stratified by race and compared to the results for the total sample.

In addition to the standardized ATP III metabolic syndrome definition examined, previous work has looked at the

Table 1: Frequency distribution (number and percent) of demographic and clinical characteristics among radical prostatectomy patients ($n = 383$).

Characteristic	All men		Recurrence		No recurrence	
	N	%	*N*	%	*N*	%
Age*	60.9	10.1	60.6	5.9	60.9	6.8
Race						
Caucasian	215	56.1	38	56.7	177	56.0
African American	168	43.9	29	43.3	139	44.0
Smoking history						
Ever	249	65.0	51	76.1	198	62.7
Never	134	35.0	16	23.9	118	37.3
Pretreatment PSA (ng/ml)						
≤10	331	86.4	50	74.6	281	88.9
>10	52	13.6	17	20.4	35	11.1
Gleason score						
≤7 (3 + 4)	280	73.1	41	61.2	239	75.6
≥7 (4 + 3)	103	26.9	26	38.8	77	24.4
Stage						
Local	321	83.8	49	73.1	272	86.1
Regional	58	15.2	15	22.4	43	13.6
Distant	4	1.0	3	4.5	1	0.3
Surgical margin status						
Positive	111	29.8	38	56.7	73	23.1
Negative	262	70.2	27	43.3	235	76.9

* Mean value with standard deviation.

Table 2: Frequency distribution (number and percent) of metabolic syndrome features among all participants ($n = 383$) and by race.

Features	All men ($n = 383$)		White men ($n = 215$)		AA men ($n = 168$)		
	N	%	*N*	%	*N*	%	*P* value*
Hypertension	216	56.4	109	50.7	107	63.7	0.01
Diabetes	56	14.6	18	8.4	38	22.6	<0.0001
Obesity	121	31.6	59	27.4	62	36.9	0.05
Low HDL cholesterol	76	22.5	52	26.7	24	16.8	0.03
High triglycerides	141	41.4	93	47.2	48	27.4	0.01
Metabolic syndrome (≥3 features)	95	24.8	49	22.8	46	27.4	0.30

* Based on Mantel-Haenszel chi-square comparing racial differences in prevalence of features.

metabolic syndrome as an accumulation of cardiometabolic abnormalities [18]. With this in mind, the number of metabolic syndrome components was also evaluated as an ordinal variable with 3 levels: 0 (referent), 1-2, and 3 or more components.

3. Results

Patient and clinical characteristics for the 383 patients included in this analysis as well as the distribution of the metabolic syndrome and its components are described in Tables 1 and 2. The mean age at time of diagnosis was approximately 61 years, and as stated earlier, over 40% of the patient population was African American. Approximately 27% of patients were considered to have high-grade disease based upon their Gleason's score with 16% of patients diagnosed with regionally advanced to distant stage disease.

Hypertension was the most commonly observed metabolic syndrome component with 56% of subjects categorized as hypertensive. There were appreciable differences in the prevalence of each component between Caucasian and African American patients (Table 2). African Americans had a higher prevalence of hypertension, obesity, and diabetes while Caucasians had a higher prevalence of low HDL and elevated triglycerides. However, there was no difference in the prevalence of metabolic syndrome overall by race.

Median follow-up time for patients in the study was 49 months (range 1 to 97 months) with 67 documented recurrences (17.5%) during the follow-up period. There was no difference between Caucasians (17.7%) and African Americans (17.3%) in the proportion of patients who recurred. The adjusted hazard ratios (HR) of BCR by metabolic syndrome component are presented in Table 3. Hypertension was associated with BCR after adjustment for patient and

Table 3: Adjusted hazard ratios (95% confidence intervals) of biochemical recurrence (BCR) by metabolic syndrome component ($n = 383$).

Feature	% of sample	Model 1	Model 2	Model 3	Model 4
Hypertension	56.4	1.9 (1.1–3.3)	1.8 (1.0–3.1)	1.7 (0.99–2.9)	2.1 (1.1–3.8)
Diabetes	14.6	1.0 (0.52–2.1)	0.99 (0.48–2.0)	1.1 (0.52–2.2)	0.99 (0.48–2.1)
Obesity	31.6	1.1 (0.63–1.8)	1.0 (0.59–1.7)	1.0 (0.60–1.8)	0.97 (0.55–1.7)
Low HDL cholesterol	22.5	0.68 (0.36–1.3)	0.57 (0.30–1.1)	0.58 (0.30–1.1)	0.48 (0.24–1.0)
High triglycerides	41.4	0.90 (0.54–1.5)	0.92 (0.54–1.6)	0.92 (0.54–1.6)	1.1 (0.64–1.7)
Metabolic Syndrome					
<3 features (referent)	75.2	1.0	1.0	1.0	
≥3 features	24.8	1.4 (0.83–2.4)	1.4 (0.85–2.5)	1.5 (0.90–2.6)	—
Ordinal Model					
0 features (referent)	23.2	1.0	1.0	1.0	
1-2 features	52.0	0.96 (0.52–1.8)	0.85 (0.45–1.6)	0.75 (0.39–1.4)	—
≥3 features	24.8	1.4 (0.70–2.7)	1.3 (0.65–2.6)	1.3 (0.63–2.5)	—

Model 1: adjusted for age and race.
Model 2: adjusted for age, race, and clinical characteristics (pre-operative PSA, Gleason's grade, tumor stage, surgical margin status).
Model 3: adjusted for age, race, clinical characteristics and smoking.
Model 4: adjusted for age, race, clinical characteristics, smoking, and other metabolic syndrome components.

clinical characteristics and the other metabolic syndrome features (HR = 2.1 (95% CI = 1.1–3.8). Low HDL level was inversely associated with the rate of BCR (Model 4: HR = 0.48; 95% CI = 0.24–1.0). Diabetes, obesity, and high triglycerides were not associated with BCR among all patients.

Adjusted hazard ratios for BCR are presented in Table 3 for two composite measures of metabolic syndrome. Treating the syndrome as a dichotomous measure (≥3 components versus <3 components), the estimated hazard ratio, adjusting for age, race, clinical characteristics, and smoking (Model 3), was 1.5 (95% CI = 0.90–2.6). Treating metabolic syndrome as an ordinal variable did not reveal any trend of increasing risk of BCR with increasing number of components.

When we stratified by race, we did not find any significant differences in the association between hypertension and BCR (Caucasian: HR = 1.9; 95% CI = 0.90–3.9 and African American: HR = 2.1; 95% CI = 0.70–6.3; P interaction = 0.91). Race-stratified estimates of the association between metabolic syndrome (≥3 components) and BCR suggest a stronger association among African Americans (HR = 1.6; 95% CI = 0.69–3.8) than Caucasians (HR = 1.2; 95% CI = 0.56–2.5). However, our sample size was inadequate to determine the significance of the differences in the association (P interaction = 0.41).

4. Discussion

Ours is the first study to examine the association between the metabolic syndrome and BCR. We observed a 50% increase in the rate of BCR among patients classified as having metabolic syndrome. That finding was primarily influenced by the apparent effect of one metabolic syndrome component—hypertension, which was associated with an approximate 2-fold increase in the rate of BCR for both white and African American men.

Approximately 18% of men had evidence for BCR based upon our definition. We found no appreciable difference in the BCR rate between African American and white men. This is similar to findings from two studies that showed race does not appear to be a risk factor for BCR [19, 20].

The positive association between hypertension and BCR was the only consistent observation among all patients across all models. Hypertension has been reported to be associated with prostate cancer risk [10] and more aggressive tumor characteristics [21]. Furthermore, antihypertensive medication is associated with a reduced risk of prostate cancer although this relation has not been examined with recurrence [22, 23]. Hypertension may promote recurrence through pathways linked to oxidative stress, whereby reactive oxygen species and low bioavailability of antioxidants have been hypothesized to promote prostate cancer cell growth [24].

Limitations of this analysis are important to consider for interpretation of the results. The study was designed to estimate the effects of genetic and environment factors on the risk of prostate cancer in a case control setting. Thus, our analysis of biochemical recurrence in a relatively small subsample of cases has limited statistical power to detect associations with the metabolic syndrome and its components, especially when adjusting for several potential confounders and stratified by patients' race. The potential presence of detection bias cannot be ruled out as men who have hypertension may be more likely to see a physician and, therefore, more likely to have PSA follow-up testing. To address this issue, we examined the frequency of PSA tests in the two-year period after surgery and found the mean number of tests between patients with and without hypertension was nearly identical (4.36 (SD = 1.81) versus 4.37 (SD = 1.93); pooled t-test $P = 0.94$). Analyses comparing postsurgery testing between men with and without metabolic syndrome (≥3 components) produced similar results ($P = 0.49$). Moreover, a previous investigation of the PSA screening behavior of these patients did not suggest any difference in the frequency of PSA testing prior to diagnosis [13].

Lipid profiles were incomplete for 45 subjects, and this missing lipid data would likely result in an underestimation of those subjects classified as having metabolic syndrome. Additionally, BMI was calculated based on self-reported height and weight. Classifications of abdominal obesity estimated by BMI could be inaccurate. Abdominal obesity is less common in African American men than other racial groups [7]. Furthermore, BMI is considered a suboptimal measure for abdominal obesity, particularly in African American men because visceral fat is most closely linked with altered lipid concentrations and insulin resistance [25].

Timing of PSA followup is another limitation of this analysis. As an observational investigation the PSA followup was done at the discretion of the treating physician and limited by subject compliance; the cases were tested for recurrence at irregular intervals. Similarly, cases with limited PSA follow-up data were excluded from our analyses. It is possible, therefore, that undetected BCR events might have biased the results if PSA followup is more or less likely to occur based upon the existence of the metabolic syndrome conditions. It is important to note, however, that there were few exclusions based upon limited data, and cases with lengthy intervals (>12 months) between PSA tests were a small proportion of subjects included.

Among the strengths of this investigation is the reliability of clinical data for determination of metabolic syndrome and BCR. Hypertension, diabetes, and lipid profiles were abstracted directly from the medical record. Additionally, PSA results were available for subjects for a median of 4 years after diagnosis. Results from prior investigations indicate the majority of localized prostate cancers that recur after radical prostatectomy are detected soon after surgery [26]. The racially diverse study population is another major strength of the investigation as the large percentage of African American participants makes it ideal to evaluate the influence of race on BCR.

5. Conclusions

This investigation was the first to evaluate metabolic syndrome and its components as predictors of the biochemical recurrence of prostate cancer after radical prostatectomy in both African American and Caucasian men. Metabolic syndrome was modestly, but not significantly, associated with increased BCR, regardless of race. Of the individual metabolic syndrome components, hypertension was consistently associated with increased BCR. Further investigations of metabolic syndrome and BCR in larger populations are needed to replicate these findings; if validated, the medical management of hypertension could influence the long-term prognosis of men with prostate cancer after definitive treatment.

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Clinical Study

Racial/Ethnic Patterns in Prostate Cancer Outcomes in an Active Surveillance Cohort

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Introduction. Concern regarding overtreatment of prostate cancer (CaP) is leading to increased attention on active surveillance (AS). This study examined CaP survivors on AS and compared secondary treatment patterns and overall survival by race/ethnicity. *Methods*. The study population consisted of CaP patients self-classified as black or white followed on AS in the Center for Prostate Disease Research (CPDR) multicenter national database between 1989 and 2008. Secondary treatment included radical prostatectomy (RP), external beam radiation therapy or brachytherapy (EBRT-Br), and hormone therapy (HT). Secondary treatment patterns and overall survival were compared by race/ethnicity. *Results*. Among 886 eligible patients, 21% were black. Despite racial differences in risk characteristics and secondary treatment patterns, overall survival was comparable across race. RP following AS was associated with the longest overall survival. *Conclusion*. Racial disparity in overall survival was not observed in this military health care beneficiary cohort with an equal access to health care.

1. Introduction

Racial/ethnic disparity in cancer outcomes has been extensively studied. With respect to prostate cancer (CaP), poorer patient outcomes among black men have been attributed to more advanced disease at the time of detection, less aggressive initial treatment, lower socioeconomic status (SES), inadequate quality and access to care, and/or more aggressive biology of the disease [1–14]. However, not all studies indicate that disparities exist. A recent meta-analysis concluded that there were no differences in CaP-specific or overall survival for white versus black men after accounting for methodological flaws of individual studies [15]. Similarly, when examining the accuracy of Partin tables for black men, Heath et al. found that race was not an independent prognostic factor for CaP progression despite higher grade and prostate-specific antigen (PSA) levels at baseline for black men [16]. Additional research has shown that once factors such as SES and treatment patterns are taken into account, observed racial disparities disappear [7, 12].

Growing concern regarding overtreatment of CaP is leading to increased interest in active surveillance (AS) as an option for patients with "low" or "very low" risk CaP. The National Comprehensive Cancer Network recommends AS for patients with "very low risk" CaP and a life expectancy of less than 20 years or men with a life expectancy of less than 10 years whose cancers are considered "low risk" [17]. The clinical dilemma becomes discerning if, and when, to intervene with secondary treatment. Factors that determine whether CaP is low, intermediate, or high risk include PSA at time of diagnosis, biopsy Gleason sum, and clinical stage at time of presentation [18]. Therefore, with the growing interest and clinical use of AS, the goal of this study was to

assess whether or not this practice carries similar risk among racial/ethnic groups.

Given the possibility that survival disparities may be a consequence of treatment modality, we examined secondary treatment patterns during the survivorship period within a cohort of patients initially followed on AS to determine whether there are differences across race/ethnicity in the following endpoints: (1) secondary treatment patterns, (2) overall survival.

2. Methods

2.1. Study Population. The study population was comprised of men enrolled in the institutional review board (IRB)-approved Center for Prostate Disease Research (CPDR) multicenter national database. A description of this cohort and related data collection activities has been described previously [19, 20]. The study sample was restricted to patients diagnosed with CaP between January 1, 1989, and December 31, 2008, and for whom initial treatment was AS. For the purposes of this study, AS was defined as the absence of treatment with curative intent for a minimum of 9 months following CaP diagnosis. Therefore, the study sample was restricted to patients with at least 9-month followup after CaP diagnosis in order to define primary treatment as AS. Only white and black patients were analyzed because of inadequate sample sizes in other racial/ethnic categories. Secondary treatment was categorized in the following manner: those who continued AS until the end of the study period (no secondary treatment); radical prostatectomy (RP); external beam radiation therapy or brachytherapy (EBRT-Br); or hormone therapy (HT) after 9 months on AS.

2.2. Demographics and Clinical Characteristics. As part of routine data collection activities of the CPDR multicenter national database, the following demographic and clinical data were recorded for each subject: age at CaP diagnosis, self-reported race (i.e., white, black), PSA at diagnosis (categorized as <10, 10–19.99, and ≥20 ng/mL), clinical T stage (T1-T2a, T2b, T2c, and T3-4), biopsy Gleason sum (2–6, 7, 8–10), number of comorbidities (categorized as 0, 1, 2, 3+), secondary treatment type (categorized as none, RP, EBRT-Br, and HT), and dates of medical services. Risk strata were estimated using the criteria of D'Amico et al [18]. This approach combines diagnostic PSA, clinical T stage, and biopsy grade into a single composite index in order to classify men into low-, intermediate-, and high-risk disease. This classification schema has been described previously [18]. In brief, low-risk patients are defined as those with the following clinical characteristics: clinical stage T1c or T2a; PSA ≤ 10 ng/mL; Gleason score ≤6. Intermediate risk patients are classified as those with clinical stage T2b; or Gleason = 7; or PSA > 10 and ≤20 ng/mL. Finally, high risk patients are those with clinical stage T2c; or PSA > 20 ng/mL; or Gleason score 8–10.

2.3. Study Endpoints. The primary study endpoint was overall survival. As part of data abstraction, vital status was reviewed annually as part of ongoing patient followup. Patient vital status was confirmed by searching the national death index using social security number, birth date, and name of the patient at the medical center where he was consented and enrolled into the database study. A secondary study endpoint included time to secondary treatment, which was calculated as the time from diagnosis with CaP to the time of initiation of RP, EBRT-Br, or HT. For patients who did not receive

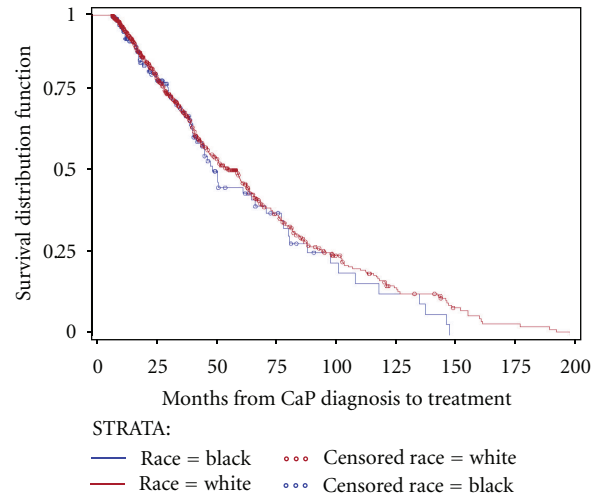

Figure 1: Kaplan Meier unadjusted estimation curve for time to secondary treatment stratified by race among subjects with prostate cancer (CaP) followed on active surveillance (AS) for primary treatment ($N = 886$).

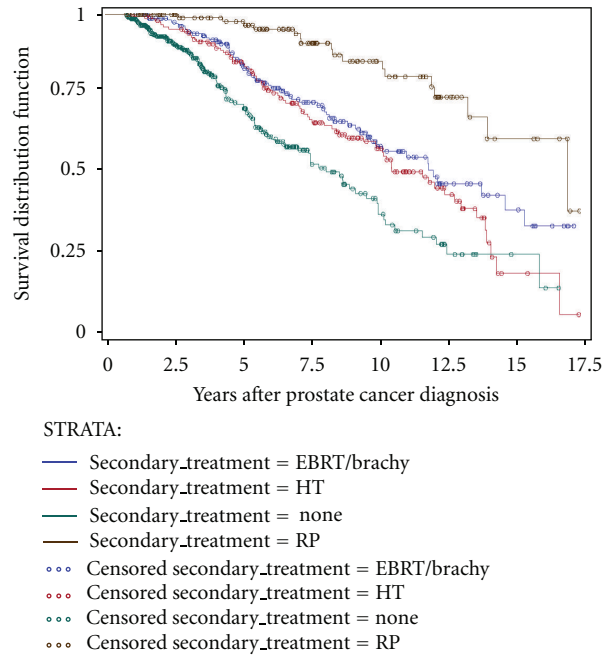

Figure 2: Kaplan Meier unadjusted estimation curve for overall survival stratified by secondary treatment type among subjects with prostate cancer (CaP) followed on active surveillance (AS) for primary treatment ($N = 886$).

Table 1: Characteristics of subjects with prostate cancer (CaP) followed on active surveillance (AS) for primary treatment, stratified by race ($N = 886$).

Race characteristic	Total $N = 886$	White $n = 696$	Black $n = 190$	P value
Age at diagnosis, years				<0.0001
Mean (±SD)[1]	69.3 (±8.4)	70.4 (±8.1)	65.3 (±8.4)	
Median (range)	70.2 (41.3–91.8)	71.7 (41.3–91.8)	65.6 (41.7–85.3)	
<60	109 (12.3)	67 (9.6)	42 (22.1)	
60–60.9	324 (36.6)	232 (33.3)	92 (48.4)	
≥70	453 (51.1)	397 (57.0)	56 (29.5)	
PSA at diagnosis, ng/mL, N (%)				<0.0001
<10	607 (68.5)	499 (71.7)	108 (56.8)	
10–19.99	153 (17.3)	115 (16.5)	38 (20.0)	
≥20	126 (14.2)	82 (11.8)	44 (23.2)	
Comorbidities, N (%)				0.1793
0	231 (26.1)	187 (26.9)	44 (23.2)	
1	264 (29.8)	205 (29.4)	59 (31.0)	
2	198 (22.3)	146 (21.0)	52 (27.4)	
≥3	193 (21.8)	158 (22.7)	35 (18.4)	
Clinical T stage, N (%)				0.1260
T1-T2a	660 (74.5)	520 (74.7)	140 (73.7)	
T2b	96 (10.8)	82 (11.8)	14 (7.4)	
T2c	68 (7.7)	49 (7.0)	19 (10.0)	
T3-4	62 (7.0)	45 (6.5)	17 (8.9)	
Biopsy grade, N (%)				0.1806
2–6	646 (72.9)	517 (74.3)	129 (67.9)	
7	168 (19.0)	127 (18.2)	41 (21.6)	
8–10	72 (8.1)	52 (7.5)	20 (10.5)	
D'Amico et al. risk strata, N (%)				0.0023
Low	434 (49.0)	359 (51.6)	75 (39.5)	
Intermediate	228 (25.7)	178 (25.6)	50 (26.3)	
High	224 (25.3)	159 (22.8)	65 (34.2)	
Secondary treatment type, N (%)				<0.0001
None (AS only)	401 (45.3)	333 (47.8)	68 (35.8)	
RP[2]	125 (14.1)	87 (12.5)	38 (20.0)	
EBRT-Br[3]	192 (21.7)	134 (19.2)	58 (30.5)	
HT[4]	168 (19.0)	142 (20.4)	26 (13.7)	
Time from Dx[5] to secondary treatment, months				0.0135
Mean (±SD)	30.6 (±26.6)	32.7 (±28.5)	24.5 (±18.6)	
Median (range)	19.6 (9.0–149.6)	20.3 (9.0–149.6)	16.0 (9.0–92.0)	
Followup, years				0.4641
Mean (±SD)	6.1 (±4.0)	6.1 (±4.0)	5.8 (±3.7)	
Median (range)	5.2 (0.8–17.2)	5.2 (0.8–17.2)	5.4 (0.8–16.8)	

[1] SD: standard deviation.
[2] RP: radical prostatectomy.
[3] EBRT-BR: external beam radiation therapy and Brachytherapy, combined.
[4] HT: hormone therapy.
[5] Dx: diagnosis of CaP.

secondary treatment, followup time is censored at the end of the study period.

2.4. Statistical Analysis. Descriptive statistics included measures of central tendency (i.e., mean, median) as well as measures of dispersion (i.e., standard deviation (SD) range). Student t tests were used to compute means in continuous patient characteristics, included age, PSA at diagnosis, and followup time. Patient characteristics were computed for the overall sample, as well as stratified for race and secondary

Table 2: Characteristics of subjects with prostate cancer (CaP) followed on active surveillance (AS) for primary treatment, stratified by secondary treatment type ($N = 886$).

Secondary treatment type characteristic	None (AS[1] only) $n = 401$	AS + RP[2] $n = 125$	AS + EBRT/Br[3] $n = 192$	AS + HT[4] $n = 168$	P value
Age at diagnosis, years					<0.0001
Mean (±SD)[5]	70.4 (±8.0)	60.7 (±7.9)	69.1 (±7.0)	73.3 (±7.0)	
Median	71.7	61.3	69.5	74.4	
Range	41.5–91.3	41.3–77.2	48.4–85.5	44.4–91.8	
PSA at diagnosis, ng/mL, N (%)					<0.0001
<10	322 (80.3)	98 (78.4)	101 (52.6)	86 (51.2)	
10–19.9	49 (12.2)	13 (10.4)	51 (26.6)	40 (23.8)	
≥20	30 (7.5)	14 (11.2)	40 (20.8)	42 (25.0)	
Race, N (%)					<0.0001
White	333 (83.0)	87 (69.6)	134 (69.8)	142 (84.5)	
Black	68 (17.0)	38 (30.4)	58 (30.2)	26 (15.5)	
Comorbidities, N (%)					0.0172
0	106 (26.4)	40 (32.0)	48 (25.0)	37 (22.0)	
1	115 (28.7)	40 (32.0)	56 (29.2)	53 (31.6)	
2	76 (19.0)	30 (24.0)	55 (28.6)	37 (22.0)	
3 or above	104 (25.9)	15 (12.0)	33 (17.2)	41 (24.4)	
Clinical T stage, N (%)					<0.0001
T1-T2a	330 (82.3)	92 (73.6)	129 (67.2)	109 (64.9)	
T2b	38 (9.5)	19 (15.2)	22 (11.5)	17 (10.1)	
T2c	21 (5.2)	10 (8.0)	15 (7.8)	22 (13.1)	
T3-4	12 (3.0)	4 (3.2)	26 (13.5)	20 (11.9)	
Biopsy grade, N (%)					<0.0001
2–6	318 (79.3)	99 (79.2)	119 (62.0)	110 (65.5)	
7	61 (15.2)	21 (16.8)	47(24.5)	39 (23.2)	
8–10	22 (5.5)	5 (4.0)	26 (13.5)	19 (11.3)	
D'Amico et al. risk strata					<0.0001
Low	246 (61.4)	68 (54.4)	61 (31.8)	59 (35.1)	
Intermediate	93 (23.2)	33 (26.4)	56 (29.2)	46 (27.4)	
High	62 (15.5)	24 (19.2)	75 (39.1)	63 (37.5)	
Time from Dx[6] to secondary treatment, months					<0.0001
Mean (±SD[5])	—	21.8 (±18.7)	25.7 (±21.3)	42.8 (±32.1)	
Median	—	14.0	16.7	34.8	
Range	—	9.0–121.2	9.0–115.0	9.2–149.6	
Followup, years					<0.0001
Mean (±SD[5])	4.2 (±3.1)	7.6 (±4.3)	7.2 (±3.9)	7.9 (±3.8)	
Median	3.4	7.4	6.4	7.5	
Range	0.7–16.5	0.8–17.2	0.8–17.0	0.9–17.2	

[1] AS: active surveillance.
[2] RP: radical prostatectomy.
[3] EBRT-BR: external beam radiation therapy and Brachytherapy, combined.
[4] HT: hormone therapy.
[5] SD: standard deviation.
[6] Dx: diagnosis of CaP.

treatment type. Mantel Haenszel chi-square tests were used to compare distributions of categorical variables by race and secondary treatment type.

Kaplan Meier (KM) unadjusted estimation curves were plotted to examine the relationships between (1) race and secondary treatment and (2) race and overall survival. KM estimation was also used to examine potential statistical interaction between race and secondary treatment in predicting overall survival patterns by producing a single KM curve for each racial group. Overall survival was then stratified by secondary treatment type.

Multivariable Cox proportional hazards modeling was used to examine overall survival, controlling for key demographics and clinical characteristics. A stratified analysis

was then conducted to examine possible effect modification between race and secondary treatment stratum ($N = 4$) with time to overall survival as the dependent outcome. Hazard odds ratio (HOR) effect estimates and corresponding 95% confidence intervals (CI) are reported. All statistical tests are 2 sided (summary alpha = 0.05), and the decision rule was based on value < 0.05. All statistical analysis was performed using SAS 9.2 (SAS Institute Inc., Cary, NC).

3. Results

Descriptive characteristics of the study sample are summarized in Tables 1 and 2, stratified for race/ethnicity and secondary treatment type, respectively. There were a total of 886 eligible patients. Twenty-one percent of the sample was black. Median age, time to secondary treatment, and followup time were 70.2, 19.6 months (1.6 years), and 5.2 years, respectively. Over two-thirds of patients had diagnostic PSA values < 10 ng/mL. Almost three-quarters of subjects (74%) had at least one comorbid condition at time of CaP diagnosis. Three-quarters of patients had clinical stage T1-T2a disease (74.8%). Biopsy Gleason sum was 2–6 for 73% of subjects. More than half of the study sample (51%) was ≥70 years of age, yet almost half (45.3%) continued AS for primary treatment throughout the study period. By D'Amico et al. risk strata, almost half of the patients were considered low risk (49.0%), while more than a quarter of patients (25.7%) were intermediate and high risk (25.3%) at time of CaP detection. For those receiving secondary treatment, 14.1% had RP, 21.7% had EBRT-Br, and 19.0% had HT.

Bivariate comparisons of sample characteristics across race demonstrate important differences (Table 1). Black men had a significantly younger mean age at CaP diagnosis (65.3 versus 70.4 years; $P < 0.0001$), a greater proportion of diagnostic PSA ≥ 10 (43.2% versus 28.3%; $P < 0.0001$), a greater proportion of high-risk disease (34.2% versus 22.8%; $P = 0.0023$), and a greater proportion of secondary treatment by RP or EBRT-Br combined (50.5% versus 31.7%; $P < 0.0001$).

Table 2 shows bivariate comparisons of sample characteristics across secondary treatment type. Patients who received RP were younger with a median age of 61 years, compared to 72, 70, and 74 years for AS only, EBRT-BR, and HT, respectively ($P < 0.0001$). Patients who received AS or RP had lower median diagnostic PSA values than those receiving EBRT-BR or HT ($P < 0.0001$). Patients who had RP were also less likely to have multiple comorbidities compared to the other treatment groups ($P = 0.017$). The secondary treatment groups with the most adverse clinical features were those who went on to receive EBRT-Br and HT ($P < 0.0001$). Those who continued to receive AS throughout the study period had a significantly shorter median followup time ($P < 0.0001$). White patients were more likely to continue using AS than black patients, whereas the latter were more likely to receive RP or EBRT-Br secondary to AS. Those who had AS-HT had significantly longer intervals between CaP diagnosis and secondary treatment (median = 35 months or 2.9 years), while those on AS-RP had the shortest interval (median = 14.9 months or 1.2 years). Interestingly, none of the black patients who received HT secondary to AS were in the youngest age group (<60 years) as compared to only 4 (6%) white patients. However, the sample of black men in this treatment stratum was very small ($n = 26$).

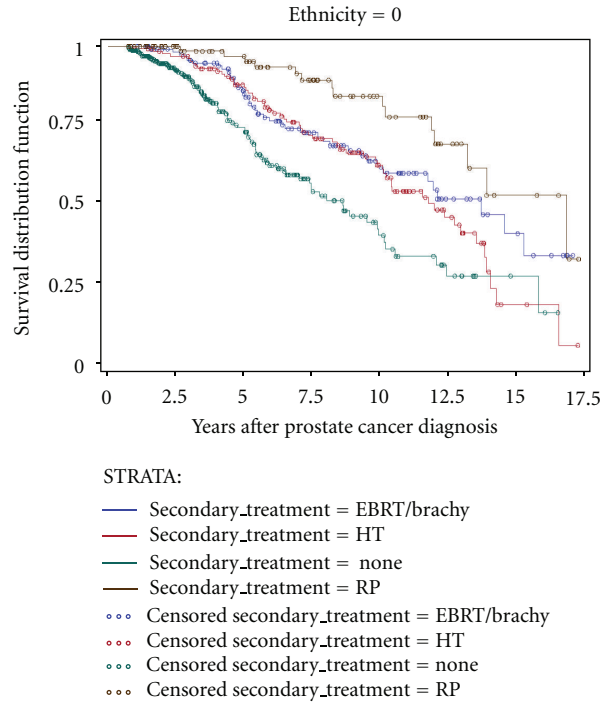

Figure 3: Kaplan Meier unadjusted estimation curve for overall survival among *white* men stratified by secondary treatment type among subjects with prostate cancer (CaP) followed on active surveillance (AS) for primary treatment ($n = 696$).

KM unadjusted time-to-event estimation curves are depicted in Figures 1–4. Time to secondary treatment was compared across race (Figure 1) revealing no statistically significant differences for black versus white patients; survival lines are parallel and roughly superimposed in the first 48 months after CaP diagnosis (log rank $P = 0.42$). Next, overall survival was examined as a function of secondary treatment type (Figure 2). This analysis was then repeated for black (Figure 3) and white (Figure 4) patients separately. Irrespective of race, a strong survival benefit was observed for patients receiving RP subsequent to AS versus all other secondary treatment groups (log rank $P < 0.0001$). In contrast, patients receiving AS only had the worst survival.

Table 3 provides findings from multivariable Cox proportional hazards regression analysis predicting overall survival. This model shows that age at diagnosis ($HOR_{(\geq 70 \text{ versus } <60)} = 1.9$, CI = 1.03–3.36, $P = 0.041$), risk stratum ($HOR_{(\text{High versus Low})} = 2.6$, CI = 1.93–3.58, $P < 0.0001$; $HOR_{(\text{Intermediate versus Low})} = 1.60$, CI = 1.16–2.24, $P = 0.0042$), secondary treatment type ($HOR_{(\text{RP versus None})} = 0.022$, CI = 0.011–0.043, $P < 0.0001$; $HOR_{(\text{EBRT-Br versus None})} = 0.052$, CI = 0.031–0.087, $P < 0.0001$; $HOR_{(\text{HTversus None})} = 0.107$, CI = 0.069–0.167, $P < 0.0001$), and time from CaP diagnosis to secondary treatment ($HOR_{(\text{per month})} = 0.97$,

Table 3: Multivariable Cox proportional hazards regression predicting overall survival in a cohort of subjects with prostate cancer (CaP) followed on active surveillance (AS) for primary treatment ($N = 886$).

Characteristic	HOR[1] (95% CI[2])	P value
Age at diagnosis, years		0.1122
<60	Referent	—
60–60.9	1.837 (1.016–3.322)	0.0441
≥70	1.856 (1.026–3.357)	0.0408
Race		
White	Referent	—
Black	1.106 (0.805–1.519)	0.5362
Comorbidities		0.2714
0	Referent	—
1	1.235 (0.877–1.738)	0.2271
2	1.029 (0.700–1.512)	0.8847
3 or more	1.373 (0.952–1.978)	0.0895
D'Amico et al. risk strata		<0.0001
Low	Referent	—
Intermediate	1.612 (1.162–2.237)	0.0042
High	2.627 (1.927–3.580)	<0.0001
Secondary treatment type		<0.0001
None (AS only)	Referent	—
RP[3]	0.022 (0.011–0.043)	<0.0001
EBRT-Br[4]	0.052 (0.031–0.087)	<0.0001
HT[5]	0.107 (0.069–0.167)	<0.0001
Dx[6] to secondary treatment, months	0.970 (0.965–0.976)	<0.0001

[1]HOR: hazard Odds Ratio.
[2]CI: confidence Interval.
[3]RP: radical prostatectomy.
[4]EBRT-BR: external beam radiation therapy and Brachytherapy, combined.
[5]HT: hormone therapy.
[6]Dx: diagnosis of CaP.

CI = 0.965–0.976, $P < 0.0001$) were significantly associated with overall survival.

Finally, multivariable Cox proportional hazards analysis predicting overall survival (Table 4) was conducted, stratified on secondary treatment type for a total of four models. These analyses show that, regardless of secondary treatment type, no racial disparity in overall survival was observed. Consistently across all 4 models, a significant predictor of overall survival was the D'Amico et al. risk classification. For three of four groups, this significant finding was restricted to comparison of risk at the extremes (i.e., high versus low). For the AS-only stratum, high D'Amico risk was associated with a 3.5 times increase odds of death from all causes ($HOR_{(High\ versus\ Low)} = 3.52$, CI = 2.18–5.69, $P < 0.0001$). Similarly, among the RP secondary treatment stratum, high D'Amico risk predicted more than a 5.5 increased odds of death ($HOR_{(High\ versus\ Low)} = 5.64$, CI = 1.48–21.4, $P = 0.011$); although the magnitude of this point estimate was large, it was also less precise due to a smaller sample size in this treatment group. Forthe EBRT-Br group, the risk comparison at the extremes was associated with over a fourfold increased odds of death ($HOR_{(High\ versus\ Low)} = 4.20$, CI = 1.98–8.90, $P = 0.0002$), while that for intermediate versus low risk demonstrated a borderline effect on survival, though it was not statistically significant: $HOR_{(Intermediate\ versus\ Low)} = 2.16$, CI = −5.3, $P = 0.020$ (Table 3). Finally, for the HT secondary treatment stratum, both comparisons of high versus low risk and intermediate versus low risk were significant in predicting overall survival: $HOR_{(High\ versus\ Low)} = 2.6$, CI = 1.4–4.8, $P = 0.0022$; $HOR_{(Intermediate\ versus\ Low)} = 2.3$, CI = 1.2–4.5, $P = 0.018$, respectively.

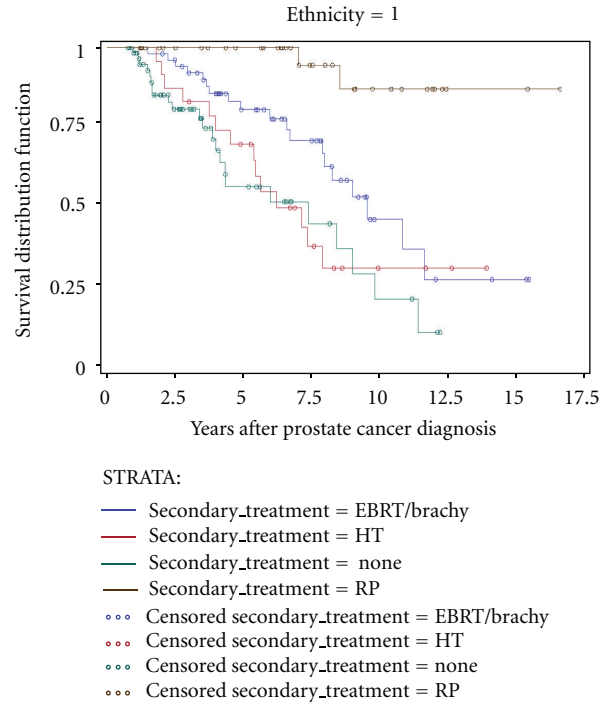

Figure 4: Kaplan Meier unadjusted estimation curve for overall survival among *black* men stratified by secondary treatment type among subjects with prostate cancer (CaP) followed on active surveillance (AS) for primary treatment ($n = 190$).

Time from diagnosis with CaP to secondary treatment was also examined in the three relevant treatment groups: AS-RP, AS-EBRT-Br, and AS-HT. For both EBRT-Br and HT as secondary treatments, there was a statistically significant effect of this time interval on overall survival such that shorter time to treatment with curative intent from EBRT-Br and HT was associated with a slightly greater odds of death from all causes ($HOR_{(per\ month)} = 0.98$, CI = 0.97–1.00, $P = 0.042$) and ($HOR_{(per\ month)} = 0.98$, CI = 0.98–0.99, $P = 0.0010$), respectively.

Multivariable Cox proportional hazards modeling was also performed stratified being by race with secondary treatment included as a model covariate in place of race, with comparable covariates entered into the secondary treatment-stratified models. In these 2 race-specific models, the lowest odds of death was observed for those who initiated RP secondary to AS for both black patients (HOR = 0.063, CI = 0.014–0.29, $P = 0.0004$) and white patients (HOR = 0.26,

Table 4: Multivariable Cox proportional hazards model predicting overall survival in a cohort of subjects with prostate cancer (CaP) followed on active surveillance (AS) for primary treatment, stratified by secondary treatment type.

Secondary treatment type characteristic	None (AS only)		RP[3]		EBRT-Br[4]		HT[5]	
	HOR[1] (95% CI[2])	*P* value	HOR (95% CI)	*P* value	HOR (95% CI)	*P* value	HOR (95% CI)	*P* value
Age at diagnosis, years		0.1737		0.1532		0.3743		0.4236
<60	Referent	—	Referent	—	Referent	—	Referent	—
60–60.9	2.43 (0.84–6.97)	0.0983	1.65 (0.35–7.60)	0.5196	1.35 (0.45–4.02)	0.5836	1.84 (0.40–8.27)	0.4264
≥70	2.700 (0.95–7.64)	0.0616	4.41 (0.85–22.7)	0.0762	1.84 (0.62–5.42)	0.2663	1.32 (0.30–5.74)	0.7108
Race								
White	Referent	—	Referent	—	Referent	—	Referent	—
Black	1.24 (0.74–2.07)	0.4120	0.46 (0.09–2.32)	0.3522	1.14 (0.64–2.03)	0.6478	1.17 (0.60–2.29)	0.6282
Comorbidities		0.3218		0.4464		0.0061		0.5145
0	Referent	—	Referent	—	Referent	—	Referent	—
1	1.15 (0.66–1.99)	0.6059	2.42 (0.65–8.99)	0.1865	0.58 (0.27–1.23)	0.1582	1.06 (0.53–2.12)	0.8657
2	1.60 (0.85–3.02)	0.1425	0.97 (0.19–4.84)	0.9731	0.48 (0.21–1.06)	0.0724	1.22 (0.60–2.46)	0.5730
≥3	1.53 (0.86–2.71)	0.1431	2.05 (0.33–12.6)	0.4361	1.70 (0.82–3.53)	0.1518	0.71 (0.34–1.50)	0.3800
D'Amico et al. risk strata		<0.0001		0.0353		0.0007		0.0787
Low	Referent	—	Referent	—	Referent	—	Referent	—
Intermediate	1.47 (0.88–2.45)	0.1371	1.78 (0.44–7.12)	0.4124	2.16 (0.99–4.71)	0.0528	1.75 (0.87–3.51)	0.1112
High	3.52 (2.18–5.69)	<0.0001	5.64 (1.48–21.4)	0.0110	4.20 (1.98–8.90)	0.0002	2.03 (1.09–3.78)	0.0257
Dx[6] to secondary treatment, months	—	—	1.00 (0.97–1.03)	0.8635	0.98 (0.97–1.00)	0.0424	0.98 (0.975–0.99)	0.0010

[1] HOR: hazard Odds Ratio.
[2] CI: confidence Interval.
[3] RP: radical prostatectomy.
[4] EBRT-BR: external beam radiation therapy and Brachytherapy, combined.
[5] HT: hormone therapy.
[6] Dx: diagnosis of CaP.

CI = 0.14–0.46, $P < 0.0001$); this effect was more pronounced in black patients (data not shown).

4. Discussion

Being black was not a predictor of poorer overall survival among participants of the CPDR multicenter national database undergoing AS as initial followup for CaP. This finding was evident despite clear racial differences in clinical characteristics at time of CaP detection. Specifically, black men were observed to have a greater proportion of intermediate- and high-risk disease, but this finding did not translate into longer-term adverse outcomes in terms of overall survival.

Interestingly, for men who underwent secondary treatment, a striking benefit was observed among the group who received RP when controlling for key clinical characteristics. Men who remained on AS had the worst survival, despite controlling for baseline risk characteristics. This is especially striking given that these patients had the shortest median followup time of only 3.4 years. This may be explained, in part, by reduced intervention with additional treatments among patients for whom death seems imminent. This is supported by the finding that patients who remained on AS, only, were more likely to have 3 or more comorbid conditions at time of CaP diagnosis.

Racial disparity in outcomes for prostate cancer survivors has been observed in several national data sources [7, 14, 21, 22]. In contrast, a recent meta-analysis concluded that there were no differences in overall or CaP-specific mortality for black versus white men with CaP [15]. Where racial differences have been noted, some researchers have proposed that variation in treatment patterns for CaP can be linked to a man's SES which in turn, may be partly to blame for observed racial disparities [4, 5, 9, 12].

Another possible explanation for racial disparity in CaP outcomes may be the geographical location or institution where health care services are received. Onega et al. found

that higher overall mortality among black versus white Medicare beneficiaries was no longer significant when restricting analysis to location of services at the National Cancer Institute cancer centers. This finding lends support to the concept that place of services may, in part, account for observed racial differences [10].

Using the Detroit Surveillance, Epidemiology, and End Results data, Powell et al. found larger average tumor volumes in black versus white men after RP as well as a 4-fold ratio of distant disease among black versus white men. The authors conclude that these findings may indicate biological differences in disease progression [11].

In 2003, an Institute of Medicine report dedicated to the topic of unequal treatment in health care in the United States found that clear and striking differences exist in the receipt of services by race/ethnicity [23]. Other researchers have noted inequity in quality and type of care by race/ethnicity as a potentially contributing cause of disparities in CaP and overall survival [2, 6].

In an examination of CaP patients of African ancestry from New York, Guyana, and the Republic of Tobago and Trinidad, Mutetwa et al. found sharp survival rate disparity between Caribbean-born men diagnosed with CaP versus New York residents. However, immigrant Caribbean-born men had survival rates that approximated those of men from New York [8]. These findings argue for the importance of environmental factors in influencing outcomes for CaP survivors. This finding could include early detection of CaP, SES and receipt of treatment, location of health care services, and other factors not yet elucidated. When examining the interrelationships between race, SES, and treatment, Schwartz et al. found that much of the survival disadvantage for black men could be explained by a combination of low SES and receipt of nonsurgical treatment for disease [12].

In our study, we examined military health care beneficiaries participating in the CPDR multicenter national database. Patients in the CPDR database study constitute a screened cohort with regular PSAs and digital rectal examinations, in conjunction with annual physical examination beginning at age 40. Therefore, lack of racial/ethnic disparity in overall survival in this study sample may be, in part, attributable to accessibility to health care services. In the face of poorer baseline risk profiles among our black subjects, the observation of comparable survival outcomes may be explained by the shorter time to secondary treatment among black men, coupled with the preferential choice of RP secondary to AS among black. This explanation is consistent with our finding that the best overall survival was observed among men who received RP after AS.

4.1. Study Considerations. Despite important work that underscores the importance of SES in the relationship between race and survival, the CPDR does not systematically collect data on income or education. The closest correlation of SES in the CPDR cohort would be a patient's military rank, which was not available for this study. Albeit, patients included in this study are those eligible for military health care regardless of their education, income, or region of the country in which they receive services. While SES cannot be ruled as out as an explanatory factor in the absence of racial disparities in this cohort, we believe there is relative homogeneity with respect to SES in our cohort regardless of race.

A clear advantage to this study is the proportion of black men included. The CPDR database has an overrepresentation of black men—roughly 20%—compared to a 2010 national average of 13.5% [24]. As mentioned, we could not examine other racial/ethnic minorities such as Asian/Pacific Islanders and Hispanics as sample sizes because these groups are not large enough in the CPDR database to model the study endpoints of interest.

The key strengths of this study are the CPDR multicenter national database cohort itself, which contains a large proportion of black patients. Also, this cohort is coupled with long-term followup of its enrollees and strong adherence to receipt of care within the equal-access military health care system. These factors make the CPDR multicenter national database an excellent resource in which to examine racial patterns in CaP outcomes.

4.2. Future Directions. Further investigation is needed to explore why younger black men with higher-risk disease are opting for AS for initial treatment. Furthermore, we need a better understanding of what influences secondary treatment decisions. In spite of disparities in secondary treatment choices, study outcomes among patients receiving AS for primary treatment did not differ across race, despite racial differences in baseline clinical risk characteristics.

Subsequent work in this expanding cohort of men will examine the specific patterns of health care delivery and use with regard to CaP. Studies of this nature will allow us, over time, to better understand how military health care beneficiaries are diagnosed and treated in our equal-access system after a CaP diagnosis.

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Clinical Study

Development and External Validation of a Nomogram Predicting the Probability of Significant Gleason Sum Upgrading among Japanese Patients with Localized Prostate Cancer

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Objective. The aim of this study is to develop a prognostic model capable of predicting the probability of significant upgrading among Japanese patients. *Methods*. The study cohort comprised 508 men treated with RP, with available prostate-specific antigen levels, biopsy, and RP Gleason sum values. Clinical and pathological data from 258 patients were obtained from another Japanese institution for validation. *Results*. Significant Gleason sum upgrading was recorded in 92 patients (18.1%) at RP. The accuracy of the nomogram predicting the probability of significant Gleason sum upgrading between biopsy and RP specimens was 88.9%. Overall AUC was 0.872 when applied to the validation data set. Nomogram predictions of significant upgrading were within 7.5% of an ideal nomogram. *Conclusions*. Nearly one-fifth of Japanese patients with prostate cancer will be significantly upgraded. Our nomogram seems to provide considerably accurate predictions regardless of minor variations in pathological assessment when applied to Japanese patient populations.

1. Introduction

Pretreatment prostate-specific antigen (PSA) level, Gleason score, and pathological stage are generally recognized as significant predictors of biochemical recurrence in patients with clinically localized prostate cancer treated by radical prostatectomy (RP) [1]. A finding of high-grade disease in RP specimens is an adverse prognostic factor, and such tumors are significantly more likely to progress than organ-confined cancers. In addition, this finding is associated with a greater risk of positive surgical margins, further decreasing the likelihood of long-term cancer control. Determining whether a patient has high-grade disease is thus important for treatment selection and prognosis [2].

Chun et al. developed and validated a model predicting Gleason sum upgrading from biopsy to final pathology using clinical variables (PSA level, clinical stage, and biopsy Gleason sum) [3]. That model relies on three readily available clinical variables, all of which are significant uni- and multivariate predictors of biopsy Gleason sum upgrading. Based on the importance of the concept of Gleason sum upgrading in decision making for prostate cancer, we previously performed a formal external validation using a fully independent data set in a contemporary cohort of two Japanese institutions [4]. Unfortunately, our results did not suggest that accurate predictions may be expected when using this nomogram across different racial patient populations. Development of a nomogram predicting the probability of biopsy Gleason sum upgrading in a large

multi-institutional cohort among Japanese patients thus appears essential.

2. Material and Methods

Clinical and pathological data were prospectively gathered from 837 consecutive patients at two centers (Department of Urology in the Graduate School of Medicine at Chiba University, Chiba ($n = 327$) and Division of Urology at Chiba Cancer Center, Chiba ($n = 510$)). Of these, 71 patients were excluded because of missing data.

Analyses targeted 766 evaluable patients assessed with ≥10 biopsy cores. All men had biopsy-confirmed, clinically localized prostate cancer, and all underwent RP between January 2003 and December 2009. Patients treated with neoadjuvant hormonal therapy were excluded, as the nomogram is not applicable in these men.

Clinical stage was assigned by the attending urologist according to the 2002 TNM system. Under transrectal ultrasound (TRUS) guidance, 10–16 needle cores were obtained. Pretreatment PSA levels were measured before a digital rectal examination (DRE) and TRUS. Biopsy Gleason sum was assigned by pathologists from each center. All RP specimens were processed according to the Stanford protocol and graded according to the Gleason system [5].

Significant upgrading was defined as a biopsy Gleason sum changing from ≤6 to ≥7 or from 7 to ≥8, according to previous reports by King [6] and King and Long [7]. For both patient cohorts, the same predictors, that is, PSA level, primary and secondary biopsy Gleason score, and clinical stage, were used in uni- and multivariate logistic regression models addressing the rate of significant Gleason sum upgrading between biopsy and RP pathology. Coefficients of multivariate logistic regression models were then used to develop a nomogram predicting the probability of significant Gleason sum upgrading, using the data from one Japanese institution: the Division of Urology at Chiba Cancer Center, Chiba ($n = 508$). The variables were selected for the final multivariate model by forward stepwise selection. In addition, we utilized the bootstrapping method to correct for overfit and the bias-corrected coefficients obtained from multivariate analysis to construct the final nomogram. Accuracy of the nomogram was quantified using the receiver operating characteristics (ROC) curve.

Validation data representing men treated with RP were obtained from another Japanese institution: the Department of Urology in the Graduate School of Medicine at Chiba University, Chiba ($n = 258$). To determine the nomogram-predicted probability of significant Gleason sum upgrading, we applied the nomogram (Figure 1) to all 258 observations. Accuracy of the nomogram was then quantified using the area under the curve (AUC) for external validation. The extent of over- or underestimation relative to the observed rate of significant upgrading was explored graphically using nonparametric Loess smoothing plots. All tests were two sided with a significance level set at $P < .05$.

3. Results

Table 1 lists the clinical and pathological characteristics of patients included in this study, and data were stratified for participating institutions. Pretreatment PSA levels were 2.5–79.7 ng/mL. Clinical stages T1c and T2 were recorded in 685 patients (89.4%). Among all men, 578 (75.5%) showed a biopsy Gleason sum of 6 or 7.

In the Chiba Cancer Center dataset (508 men), concordance between biopsy and RP Gleason sum was recorded in 258 (50.8%). Upgrading was recorded in 104 men (20.5%), whereas 146 (28.7%) were downgraded. These data also indicate that 69 patients (13.6%) were upgraded from biopsy Gleason sum ≤6 to pathologic Gleason sum ≥7. The rate of upgrading from biopsy Gleason sum 7 to pathologic Gleason sum ≥8 was 4.5% ($n = 23$). The overall rate of significant upgrading from biopsy to pathologic Gleason sum was 18.1% (92 patients). Conversely, Gleason sum decreased from ≥8 to ≤7 in 82 men (16.1%) and from 7 to ≤6 in 36 (7.1%). Stratified according to institutions, agreement between Gleason biopsy and final pathology was more frequent in the Chiba University data set (146 men, 56.6%) than in that from Chiba Cancer Center (50.8%). Significant upgrading was more frequent for Chiba University (64 men, 24.8%) than for Chiba Cancer Center (92, 18.1%). We also investigated temporal changes in the rate of significant Gleason sum upgrading for two institutions. Although no significant correlation was found, a trend toward a decrease in the rate of significant upgrading since 2006 was seen.

Table 2 shows uni- and multivariate logistic regression models for PSA, clinical stage, and primary and secondary biopsy Gleason scores with corresponding uni- and multivariate predictive accuracy estimates. Clinical stage was not associated with significant upgrading in univariate analysis ($P = .131$) and was excluded for multivariate analyses. In univariate analyses, primary and secondary biopsy Gleason scores were highly significant predictors of significant Gleason sum upgrading ($P < .001$ and $P = .002$, resp.). Of all predictors, secondary biopsy Gleason score (AUC = 0.784) represented the most informative predictor, followed by primary biopsy Gleason score (AUC = 0.712) and PSA (AUC = 0.569). In multivariate analyses, all variables except for clinical stage were highly significant ($P \leq .001$). Multivariate 200 bootstrap-corrected predictive accuracy was 88.9% and exceeded the most informative univariate predictor, namely secondary biopsy Gleason score (78.4%). Figure 1 shows the regression coefficient-based nomogram. High PSA values as well as low primary and/or secondary biopsy Gleason scores are risk factors for significant Gleason sum upgrading at final pathology.

Figure 2 illustrates how predictions of the nomogram are compared with actual probabilities for the validation data (258 men). The x-axis represents nomogram predictions, and the y-axis represents the observed rate of significant Gleason upgrading for patients in the validation cohort. Accuracy of the nomogram was 87.2% (confidence interval, 82.7–91.7%). The dashed 45° line represents the performance of an ideal nomogram, where predicted outcome would correspond perfectly with actual outcome.

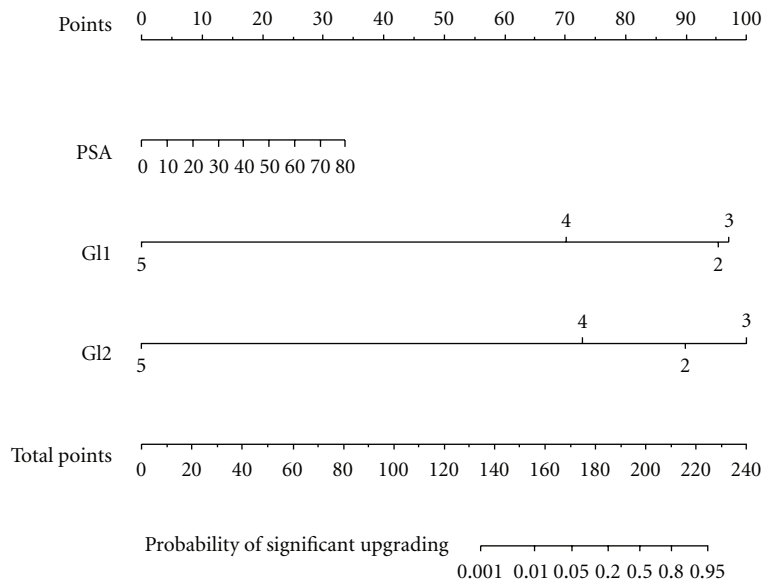

Figure 1: Nomogram based on 508 patients treated at Chiba Cancer Center, for predicting significant Gleason sum upgrading between biopsy and radical prostatectomy. PSA: prostate-specific antigen (ng/mL); Gl1: primary biopsy Gleason score; Gl2: secondary biopsy Gleason score. To obtain the nomogram-predicted probability of significant biopsy upgrading, locate the patient values at each axis, draw a vertical line to the "Points" axis to determine how many points are attributed to each variable value; total the points for all variables, and locate the sum on the "Total Points" line to assess the individual probability of significant biopsy Gleason sum upgrading on the Probability of Significant Upgrading line.

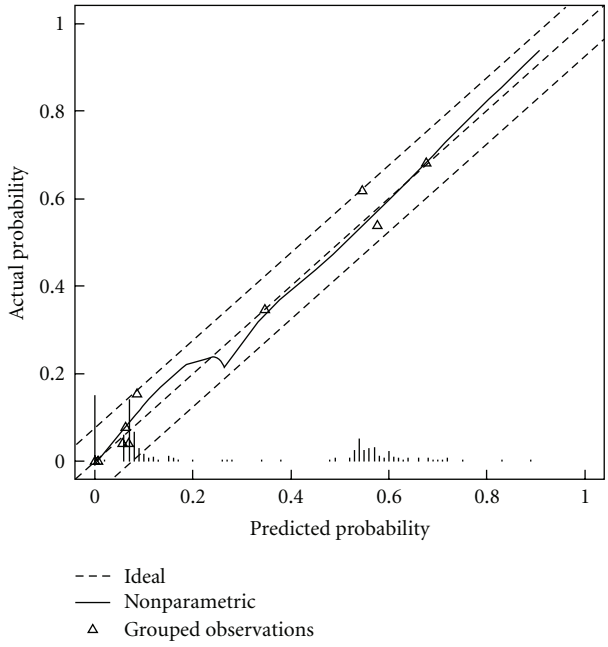

Figure 2: Calibration plot for external validation cohort. The x-axis shows the prediction calculated using the nomogram, and the y-axis gives observed rates of significant Gleason sum upgrading for patients in the validation cohort. Dashed line indicates reference line, where an ideal nomogram would lie. Solid line indicates performance of the nomogram applied to the validation cohort. The solid line is close to the dashed line of the ideal nomogram and is always within the 7.5% margin of error.

The performance of our nomogram is plotted as the solid line. The dotted lines represent a 7.5% margin of error, and the nomogram calibration plot demonstrated virtually ideal predictions. The rate of predicted significant Gleason upgrading closely paralleled the observed rate of Gleason upgrading, nearly corresponding to the 45° line and always within the 7.5% margin of error. The correspondence seen between actual and ideal nomogram predictions suggests good calibration of the nomogram in the validation cohort.

4. Discussion

Biopsy upgrading has important clinical implications in terms of watchful waiting, surgery, and radiotherapy (RT) candidates [8–10]. Most reported biopsy Gleason sums are either 6 or 7, and these Gleason sums are at greatest risk of being upgraded. However, tools have previously been unavailable for reliably and accurately predicting this phenomenon. Previous reports have indicated that with more extended biopsy schemes, the risk of upgrading decreases [8, 11] due to higher sampling density and more accurate evaluation of the pathological biopsy. Extended biopsy schemes (≥10 cores) might affect the rate of and ability to predict biopsy Gleason sum upgrading [12]. As a result, ≥14 needle cores are currently obtained in our institutions [13].

King [6] and King and Long [7] defined significant Gleason sum upgrading as a Gleason sum increase either from ≤6 to ≥7 or from 7 to ≥8 between biopsy and

Table 1: Descriptive characteristics of subgroups according to institutions.

Variable		Chiba Cancer Center	Chiba University
n		508	258
Age (years)	Mean	66.902	65.054
	SD	4.975	5.253
	Median	67	65
	Min	52	49
	Max	78	76
PSA (ng/mL)	Mean	13.977	11.616
	SD	12.194	9.732
	Median	9.755	8.420
	Min	2.588	2.450
	Max	79.710	72.000
Clinical stage (%)	T1c	169 (33.3)	180 (69.8)
	T2a	172 (33.9)	32 (12.4)
	T2b	89 (17.5)	15 (5.8)
	T2c	12 (2.4)	16 (6.2)
	T3	66 (13.0)	15 (5.8)
Biopsy Gleason primary (%)	≤3	318 (62.6)	172 (66.7)
	4	167 (32.9)	80 (31.0)
	5	23 (4.5)	6(2.3)
Biopsy Gleason secondary (%)	≤3	197 (38.8)	128 (49.6)
	4	227 (44.7)	112 (43.4)
	5	84 (16.5)	18 (7.0)
Biopsy Gleason sum (%)	≤6	123 (24.2)	91 (35.3)
	7	248 (48.8)	116 (45.0)
	8	58 (11.4)	31 (12.0)
	9	74 (14.6)	18 (7.0)
	10	5 (1.0)	2 (0.8)
Pathological Gleason primary (%)	≤3	327 (64.4)	151 (58.5)
	4	155 (30.5)	104 (40.3)
	5	26 (5.1)	3 (1.2)
Pathological Gleason secondary (%)	≤3	209 (41.1)	114 (44.2)
	4	241 (47.4)	119 (46.1)
	5	58 (11.4)	25 (9.7)
Pathological Gleason sum (%)	≤6	93 (18.3)	44 (17.1)
	7	332 (65.4)	176 (68.2)
	8	21 (4.1)	11 (4.3)
	9	60 (11.8)	27 (10.5)
	10	2 (0.4)	0 (0.0)
Significant upgrading Gleason sum (%)		92 (18.1)	64 (24.8)

Table 2: Uni- and multivariate logistic regression models predicting significant Gleason sum upgrading.

Predictors	Univariate predictive	Univariate model		Multivariate model	
	accuracy	OR	*P*	OR	*P*
Preoperative PSA	0.569	1.020	.025	1.047	<.001
Clinical stage	NA				
1c		1.000			
2a		0.978	.934	NA	NA
2b		0.715	.334	NA	NA
2c		0.000	.983	NA	NA
3		0.528	.131	NA	NA
Biopsy Gleason primary	0.712				
2		1.000			
3		0.250	<.001	1.210	.677
4		0.041	<.001	0.064	<.001
5		0.000	.983	0.000	.992
Biopsy Gleason secondary	0.784				
2		1.000			
3		1.491	.435	3.050	.041
4		0.189	.002	0.156	.001
5		0.000	.98	0.000	.986
Predictive accuracy				0.889	

OR: odds ratio; PSA: prostate-specific antigen; NA: not assessed.

RP specimens. They distinguished between any upgrading and significant upgrading and suggested that significant upgrading represents a clinically meaningful entity. Predicting the rate of significant upgrading would be much more clinically meaningful, since these three categories represent pathologically and clinically different diseases. A preparative nomogram predicting the probability of significant Gleason sum upgrading was developed among Western populations [14]. Given the utility of the concept, creation of a new prediction tool based on a modern, Japanese-only cohort and aimed at predicting significant upgrading represents a worthwhile goal.

These findings are important as a first substantial depiction of the rate of significant Gleason sum upgrading in a Japanese contemporary cohort. Several applications of these findings can be considered. For example, the choice of interstitial brachytherapy might be reconsidered in men who are at greater risk of biopsy Gleason sum upgrading. Similarly, neoadjuvant hormonal therapy might be considered if radiotherapy is contemplated. Finally, among surgical candidates, the risk of significant Gleason sum upgrading might contribute to different considerations regarding the extent of neurovascular bundle resection and the implications of positive surgical margins. However, the decision of what level of risk is required for more aggressive therapy remains controversial.

Chun et al. indicated that the rate of upgrading decreased over time [3]. We also investigated temporal changes in the rate of significant Gleason sum upgrading and found no

significance. However, a trend toward a decreased rate of significant upgrading over time since 2006 was apparent. This decrease may be due to the impact of the 2005 International Society of Urological Pathology (ISUP) modified Gleason grading system [15]. A shift towards a higher Gleason sum on biopsy might also have occurred after the ISUP consensus [16].

Prostate cancer is one of the most common cancers among Western populations, and incidence is increasing in Asia, although considerable differences in incidence and biological aggressiveness remain between Western and Asian populations [17]. Epidemiological and genetic differences in prostate cancers exist between patients in Japan and the United States, and p53 gene mutational analysis, which often provides information about etiological factors, has revealed clear differences in p53 gene mutational spectra between Japanese and Western cases [18]. Differences in hormone levels in various racial/ethnic groups have been suggested to account for part of the differences in prostate cancer risk. Racial/ethnic differences in the intraprostatic testosterone/dihydrotestosterone conversion ratio would provide important support for the hypothesis that differences in the enzymatic activity of 5a-reductase within the prostate gland can explain most of the racial/ethnic differences in prostate cancer risk [19–21].

We have previously performed a formal external validation of a preparative nomogram predicting the probability of Gleason sum upgrading developed among Western populations, using a fully independent data set in a contemporary cohort of two Japanese institutions [4]. The nomogram provided reasonably accurate predictions regardless of minor variations in pathological assessment but could not necessarily be considered accurate when applied to Japanese patient populations. Our previous results suggested that development of a nomogram predicting the probability of biopsy Gleason sum upgrading in a large multi-institutional cohort among Japanese patients is essential.

We are the first to develop multivariate models to predict significant Gleason sum upgrading between biopsy and RP in Japanese populations. Our current model was 88.9% accurate in predicting the probability of significant Gleason sum upgrading. To date, no other models capable of accurately predicting the rate of significant upgrading are available for Japanese patients. Consequently, this model represents the only alternative to clinical ratings of the probability of significant Gleason sum upgrading. We have therefore tested the performance of the nomogram in an external validation dataset, and overall AUC was 0.87. Individual treatment centers in this study differed with respect to patient selection, extracapsular extension measurement, and follow up assessment. Furthermore, no centralized review of pathology was performed. For the purposes of nomogram validation, such heterogeneity is desirable to gain insights into how the nomogram will perform across varied settings [22]. The nomogram was consistently accurate at both centers, with AUC ranging from 0.87 to 0.89. Our nomogram thus seems to provide reasonably accurate predictions regardless of minor variations in pathological assessment.

Clear limitations exist to this study. We included 10–16 core biopsy data in the cohort, but the difference in rate of upgrading was not significant between these biopsy regimens according to the current data [14]. However, biopsy schemes that rely on taking even more cores might be associated with a lower rate of biopsy Gleason sum upgrading [23–25]. In addition to the small population size, the level of experience of pathologists could also affect the findings. Finally, model accuracy could potentially be improved by integrating additional predictor variables, for example, the level of expertise of the pathologist, or existing biomarkers [26]. If the ISUP modified Gleason grading system or central pathology diagnosis system was introduced, this nomogram should be more useful for daily clinical practice. Despite these limitations, our model represents an important contribution concerning the rate of significant Gleason sum upgrading between biopsy and final pathology.

5. Conclusions

Significant Gleason sum upgrading between biopsy and final pathology represents an important consideration in treatment decision making, even in most contemporary patients. Our nomogram was 88.9% accurate in predicting the probability of significant Gleason sum upgrading, and seems to provide accurate predictions regardless of minor variations in pathological assessment when applied to Japanese patient populations.

Abbreviations and Acronyms

RP: Radical prostatectomy
AUC: Area under the receiver operating characteristic curve
PSA: Prostate-specific antigen
TRUS: Transrectal ultrasound
DRE: Digital rectal examination
ROC: Receiver operating characteristics
RT: Radiotherapy
ISUP: International Society of Urological Pathology.

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