Published in final edited form as:
J Urol. 2010 May ; 183(5): . doi:10.1016/j.juro.2010.01.015.

Evidence Supports a Faster Growth Rate and/or Earlier Transformation to Clinically Significant Prostate Cancer in Black Than in White American Men and Influences Racial Progression and Mortality Disparity

Isaac J. Powell[*], **Cathryn H. Bock**, **Julie J. Ruterbusch**, and **Wael Sakr**
Wayne State University School of Medicine and Karmanos Cancer Institute, Detroit, Michigan

Abstract

Purpose—The incidence of prostate cancer is approximately 60% higher and the mortality rate is 2 to 3 times greater in black than in white American men. We propose that a more rapid prostate cancer growth rate and/or earlier transformation from latent to aggressive prostate cancer in black than in white men contribute to this disparity.

Materials and Methods—We evaluated entirely embedded prostate glands on autopsy from 1,056 black and white men who died of causes other than prostate cancer. We also reviewed data from our radical prostatectomy database and from the Detroit Surveillance, Epidemiology and End Results database.

Results—Autopsy data indicated that sub-clinical prostate cancer in black and white men starts at early age and clinical characteristics do not differ by race at early ages. Radical prostatectomy specimen data revealed that prostate cancer volume and Gleason grade were greater in black than in white men. Advanced or meta-static prostate cancer occurred at a 4:1 ratio in black and white men, respectively, in the Detroit Surveillance, Epidemiology and End Results registry database.

Conclusions—Results showed that age at prostate cancer initiation and clinical characteristics did not differ by race in our autopsy series, prostate cancer volume after radical prostatectomy was greater in black than in white men and disease became distant disease at a ratio of 4 black men to 1 white man in the Detroit Surveillance, Epidemiology and End Results population. These findings support the concept that prostate cancer grows more rapidly in black than in white men and/or earlier transformation from latent to aggressive prostate cancer occurs in black than in white men.

Keywords

prostate; prostatic neoplasms; African continental ancestry group; European continental ancestry group; disease progression

The incidence of PCa is approximately 60% higher and the mortality rate is 2 to 3 times greater in AAM than in EAM. These findings have been consistent for more than 20 years, before and after the PSA era.[1] Men of West African ancestry from the Caribbean and South America share incidence and mortality similar to those of AAM, suggesting a possible

[*]Correspondence: Department of Urology, 4201 St. Antoine, 7C UHC, Detroit, Michigan 48201 (telephone: 313-577-5222; FAX: 313-577-5217; ipowell@med.wayne.edu).

genetic basis of these outcomes. [2] However, multiple factors probably contribute to these disparities.

Lack of access to care was suggested as responsible for disproportionate advanced disease and mortality in AAM compared to EAM. Data from the Behavioral Risk Factor Surveillance Study indicate that in recent years AAM are as likely to be tested for PCa by PSA as EAM (59.6% vs 55.5%).[3] However, AAM continue to present with more advanced disease and a higher mortality rate. Financial barriers or the lack of insurance were also suggested as potential causes of the disparity. According to the Behavioral Risk Factor Surveillance Study insurance rates for AAM and EAM older than 50 years are 81% and 89%, respectively.[3] That difference is statistically significant but in our opinion does not account for the entire disparity. Perhaps it may only contribute to a small difference in access to care, as shown by the similar PSA testing rate.

SES was also reported as a factor contributing to PCa racial disparity but this issue is controversial. Studies that examined SES on multivariate analysis showed that SES does contribute to the racial outcome disparity.[4,5] However, no difference in PCa recurrence after radical prostatectomy was identified in AAM when comparing lower vs middle incomes. [6] Non-financial barriers such as poor health seeking behavior were reported to delay PCa diagnosis in AAM. Fear of the PCa diagnosis and distrust of the health care system appear to be the most dominant factors.[7] Evidence shows that PCa treatment differences contribute to the survival disparity. AAM are less likely to be treated for PCa than EAM for similar disease stages.[8]

We propose that a more rapid PCa growth rate and/or earlier transformation from latent to aggressive PCa in AAM than in EAM contribute significantly to the racial disparity of advanced disease at diagnosis and to the 2 to 3 times greater mortality rate in AAM than in EAM. We examined our autopsy series RP results from our institutions and Detroit SEER data to study this issue.

METHODS

Prostate Tissue Autopsy Study

A collaborative effort between the Wayne State University Medical School department of pathology and the Medical Examiner's Office of Wayne County, each in Detroit, Michigan, resulted in a contemporary autopsy study, of which the results were last updated in a 2005 report.[9,10] The most recent data set comprises information on 1,056 prostate glands from consecutively autopsied AAM and EAM from 20 to 80 years old through the Medical Examiner's Office from 1992 to 2001. The glands were step sectioned perpendicular to the posterior rectal surface at 2.5 mm intervals. The resulting tissue slices were embedded as whole mount paraffin blocks, from which 5 μ hematoxylin and eosin stained sections were obtained.

Microscopic evaluation included thorough analysis of the entire gland for adenocarcinoma. Carcinoma foci were mapped on individual specimen diagrams with the Gleason score of each focus, including primary and secondary patterns as applicable, and recorded. The microscopic dimension of the focus was documented using a micrometer. Total cancer volume in glands harboring PCa was then calculated by adding the volumes of the individual foci. Clinically significant cancer was defined as greater than 0.5 cm. A collective final Gleason score was also documented for such specimens.

HGPIN areas were identified and mapped on the diagram. The degree of HGPIN involvement was graded as focal, multi-focal or extensive based on whether the lesion was

present in 1 or 2, 3 to 5 or more than 5 foci, respectively. The HGPIN focus was determined to be spatially associated with carcinoma when the 2 were present in a single 10× microscopic field.[11]

RP Prostate Tissue Study

A total of 2,874 men 39 to 77 years old underwent RP at Karmanos Cancer Institute from 1991 to 2007. Men who received neoadjuvant therapy were excluded from study. RP specimens were prepared and examined using methods similar to those described for autopsy specimens.

SEER Data Analysis

We used Detroit SEER limited use data files for 1995 to 2004 and the statistical program SEER*Stat to calculate age specific PCa incidence rates for distant disease.[12] The SEER program uses the terms black and white to describe race. However, the genetic and biological literature considers ancestral geographic origin a better description of race. Most patients classified as white race in the SEER data are of European origin, and for the purpose of this analysis and discussion we translated white race to European American. Rate ratios were calculated by comparing incidence rates between EAM and AAM.

RESULTS

Autopsy study in 1,056 men who died of causes other than PCa between 1993 and 2004 indicated that PCa began as early as ages 20 to 29 years and the prevalence was similar in AAM and EAM (8% and 11%, respectively) (table 1). Results showed that the prevalence of mostly latent or sub-clinical PCa at autopsy increased with age, as we would expect, and the prevalence continued to be similar between the 2 races.

The autopsy series revealed that HGPIN also began as early as ages 20 to 29 years and the HGPIN prevalence was similar in AAM and EAM (7% and 8%, respectively) (table 2). However, the prevalence of extensive HGPIN was significantly greater in AAM who were 40 to 49 years old or older than in EAM of similar ages (46% vs 29%).

PCa autopsy volume in AAM was similar to that in EAM at ages 20 to 60 years and grade was similar at ages 20 to 70 years (table 1). However, RP specimen PCa volume was greater in AAM than in EAM at ages 39 to 70 years (table 3). EAM had greater PCa volume than AAM in autopsy and RP specimens at older ages. Of men 40 to 69 years old AAM had marginally higher Gleason grade than EAM (6 or lower vs 7 or higher, $p = 0.0562$). In 1992 to 1998 AAM had significantly higher Gleason grade than EAM ($p = 0.028$).

In Detroit SEER data the age specific incidence rate of distant PCa/100,000 men was approximately 4 times greater in AAM than in EAM for all age groups (table 4). Thus, PCa starts at the same time in AAM and EAM but becomes distant meta-static disease at a disproportionate rate of 4:1 in AAM to EAM beginning at ages 40 to 49 years.

DISCUSSION

Our autopsy study revealed that PCa volume is similar in young (ages 20 to 60 years) AAM and EAM. Grade is also similar. However, of men who underwent RP the AAM had greater PCa volume and higher grade tumors than the EAM at ages less than 70 years. Evidence suggests that PCa grows more rapidly and shows earlier transformation from latent to aggressive disease in AAM than in EAM.

Sanchez-Ortiz et al reported that AAM with non-palpable PCa had higher prostatectomy Gleason scores, greater cancer volume and greater tumor volume per ng/ml serum PSA.[13] If PCa starts at the same time as in our autopsy study but achieves distant metastasis at a disproportionate rate of approximately 4:1 in AAM vs EAM, one may also conclude that the cancer grows more rapidly in AAM than in EAM. Alternate explanations for the conclusion is that the PCa growth rate is identical in AAM and EAM but PCa begins to grow earlier in AAM. Thus, one may assume that clinically significant PCa begins at a later age in EAM and, hence, the growth rates are the same. One also may assume that the number of aggressive or rapidly growing tumors in AAM is greater than in EAM.

A recent report concluded that extensive HGPIN is associated with an increased risk of clinically significant PCa.[14] Data suggest that at ages 40 to 49 years conversion to clinically significant PCa at disproportionate rates in AAM vs EAM may be the beginning of the PCa racial disparity. Support for these observations and conclusion are based on volume and Gleason grade analysis from the RP database revealing higher Gleason grade PCa in AAM than in EAM at early ages (40 to 49 years). This disparity continues in later decades. However, this significant development in disparity in volume, stage and grade occurred in 2 decades or less in reference to the autopsy study. Also, the fact that this disparity is prevalent in 40 to 49-year-old men minimizes if not eliminates any screening impact since screening recommendations in EAM began at age 50 years before the recent 2009 National Comprehensive Cancer Network recommended changes,[15] and at 40 and 45 years in AAM, as recommended by the American Urological Association and American Cancer Society, respectively.[16,17] Because volume and grade reflect PCa biology, the analysis implies that PCa in AAM is biologically and genetically more aggressive than in EAM. Cancer is a genetic disease, and the explanation of and answer to differences in incidence and disease progression should begin there.

Multiple genetic and biological pathways contribute to more aggressive PCa, and increased cell proliferation and metastasis in AAM than in EAM. Factors such as diet, obesity and hypertension impact PCa by association and some mechanistic processes were noted. AAM have a higher fat content diet,[18] are more obese with a higher body mass index[19] and have a higher rate of hypertension than EAM.[20] The latter 2 factors are components of metabolic syndrome. The mechanism associated with obesity and hypertension includes the release of inflammatory cytokines and reactive oxides and, thus, oxidative stress, DNA damage and NFkB activation. NFkB causes PCa cell proliferation.[21] A high fat content diet is associated with glucose-like growth factor 1 up-regulation. This also impacts NFkB via the pathway of the growth mediator V-akt murine thymoma viral oncogene homologue-1.[22] The protein NFkB activates or up-regulates androgen receptor protein expression. Gaston et al reported that androgen receptor expression is 81% higher in PCa in AAM than in EAM. Thus, PCa may develop at a younger age and progress more rapidly in AAM than in EAM due to racial differences in androgen receptor stimulation of the prostate.[23] Using microarray technology Wallace et al examined known metastasis promoting genes, including autocrine motility factor receptor, CXC chemokine receptor R4 and matrix metalloproteinase 9, and found that these genes were more highly expressed in tumors from AAM than from EAM.[24] These genes may be impacted by environmental factors, including diet, obesity and inflammation.

CYP3A4 is a protein of the cytochrome P-450 supergene family, which is involved in oxidative deactivation of testosterone to biologically less active metabolites. Inhibition of this transformation results in the increased bioavailability of testosterone, increased conversion to dihydrotestosterone and androgen receptor stimulation. A germline genetic variant in the 5′ regulatory region of the CYP3A4 gene (A to G transition) on chromosome 7 was reported and named CYP3A4*1B and CYP3A4-V. In a study in EAM only Rebbeck et al found that the genetic variant of CYP3A4 is associated with higher clinical grade and

stage PCa.[25] However, allele frequency of the variant G allele is differentially distributed across racial and ethnic groups. Powell et al reported a strong association between race and genotype ($p = 0.00002$), in that 8% of EAM and 83% of AAM had 1 or more copies of the G allele.[26] When each race was included, genotype was associated with progression-free survival ($p = 0.005$). Downstream on the chromosome 7 domain CYP3A43 cytosine-to-guanine polymorphism Bonilla et al found a highly significant association between CYP3A43 and high grade PCa in men younger than 60 years old.[27] This finding remained significant after controlling for ancestry.

Recent studies identified multiple SNPs at 8q24 associated with PCa. Most were case-control studies showing racial/ethnic specific SNPs associated with PCa.[28] Also, 4 regions were identified with different racial/ethnic distributions and ORs of SNPs associated with PCa.[29] Combinations of multiple SNPs carry a considerably larger association with PCa. Haiman et al measured population attributable risk calculations of 7 SNPs or variants and found that AAM had a significantly higher association with PCa than EAM (68% vs 32%).[28] Helfand et al reported that multiple risk alleles were significantly associated with high grade disease in biopsy and prostatectomy specimens of their cohort study population.[30]

CONCLUSIONS

Age at PCa initiation and clinical characteristics did not differ by race in our autopsy series. However, PCa volume in our patients with RP was greater in AAM than in EAM and the disease became distant disease at a ratio of 4 AAM to 1 EAM in the Detroit SEER population. These findings support the concept that PCa grows more rapidly in AAM than in EAM and/or earlier transformation from latent to aggressive PCa occurs in AAM than in EAM.

Abbreviations and Acronyms

AAM	black men
CXCR4	CXC chemokine receptor
CYP3A4	cytochrome P450 3A4
EAM	white men
HGPIN	high grade prostatic intraepithelial neoplasia
NFkB	nuclear factor κ light chain enhancer of activated B cells
PCa	prostate cancer
PSA	prostate specific antigen
RP	radical prostatectomy
SEER	Surveillance, Epidemiology and End Results
SES	socioeconomic status
SNP	single nucleotide polymorphism

REFERENCES

1. Horner, MJ.; Ries, LAG.; Krapcho, M., et al. Bethesda, Maryland: National Cancer Institute; 2009. SEER Cancer Statistics Review, 1975–2006. http://seer.cancer.gov/csr/1975_2006/ based on November 2008 SEER data submission, posted to the SEER website

2. Odedina FT, Akinremi TO, Chinegwundoh F, et al. Prostate cancer disparities in black men of African descent: a comparative literature review of prostate cancer burden among black men in the United States, Caribbean, United Kingdom, and West Africa. Infectious Agents Cancer. 2009; 4(suppl):S2. [PubMed: 19208207]
3. Behavioral Risk Factor Surveillance System Survey Data. Centers for Disease Control and Prevention. Atlanta: United States Department of Health and Human Services, Centers for Disease Control and Prevention; 2009.
4. Du XL, Fang S, Coker AL, et al. Racial disparity and socioeconomic status in association with survival in older men with local/regional stage prostate carcinoma findings from a large community-based cohort. Cancer. 2006; 106:1276. [PubMed: 16475208]
5. Ward E, Jemal A, Cokkinides V, et al. Cancer disparities by race/ethnicity and socioeconomic status. CA Cancer J Clin. 2004; 54:78. [PubMed: 15061598]
6. Dash A, Lee P, Zhou Q, et al. Impact of socioeconomic factors on prostate cancer outcomes in Black patients treated with surgery. Urology. 2008; 72:641. [PubMed: 18295314]
7. Powell IJ, Heilbrun L, Littrup PL, et al. Outcome of African-American men screened for prostate cancer: the Detroit Education and Early Detection Study. J Urol. 1997; 158:146. [PubMed: 9186342]
8. Underwood W, De Monner S, Ubel P, et al. Racial/ethnic disparities in the treatment of localized/regional prostate cancer. J Urol. 2004; 171:1504. [PubMed: 15017208]
9. Sakr WA, Ward C, Grignon DJ, et al. Epidemiology and molecular biology of early prostatic neoplasia. Mol Urol. 2000; 4:109. [PubMed: 11062364]
10. Sakr WA. personal communication.
11. Sakr WA, Grignon DJ, Hass G, et al. Age and racial distribution of prostate intraepithelial neoplasia. Eur Urol. 1996; 30:138. [PubMed: 8875194]
12. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence-SEER 9 Regs Limited-Use, Nov 2007 Sub (1973–2005) <Katrina/Rita Population Adjustment>-Linked To County Attributes-Total U.S., 1969–2005 Counties. National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Cancer Statistics Branch; released April 2008, based on the November 2007 submission.
13. Sanchez-Ortiz RF, Troncoso P, Babaian, et al. African-American men with nonpalpable prostate cancer exhibit greater tumor volume than matched white men. Cancer. 2006; 107:75. [PubMed: 16736511]
14. Merriman JL, Jones G, Walker D, et al. Multifocal high grade prostatic intraepithelial neoplasia is a significant risk factor for prostate adenocarcinoma. J Urol. 2009; 182:485. [PubMed: 19524976]
15. NCCN Clinical Practice Guidelines in Oncology™. Prostate Cancer Early Detection version 2.2010. National Comprehensive Cancer Network. Available at www.nccn.org.
16. Prostate-specific antigen (PSA) best practice policy. American Urological Association (AUA). Oncology (Williston Park). 2000; 14:267. [PubMed: 10736812]
17. Cancer Facts and Figures 2009. Atlanta: American Cancer Society; 2009.
18. Whittemorre AS, Kolonel LN, Wu AH, et al. Prostate cancer in relation to diet, physical activity, and body size in blacks, whites, and Asians in the U. S. and Canada. J Natl Cancer Inst. 1995; 87:652. [PubMed: 7752270]
19. Amling, Cl; Riffenburgh, RH.; Sun, L., et al. Pathologic variables and recurrence rates as related to obesity and race in men with prostate cancer undergoing radical prostatectomy. J Clin Oncol. 2004; 22:430.
20. Gokce N, Holbrook M, Duffy SJ, et al. Effect of race and hypertension on flow-mediated and nitroglycerin- mediated dilatation of the brachial artery. Hypertension. 2001; 38:1349. [PubMed: 11751716]
21. Sonnenberg GE, Krakower GR, Kissebah AH. A novel pathway to the manifestations of metabolic syndrome. Obes Res. 2004; 12:180. [PubMed: 14981209]
22. Hsing AH, Sakoda LC, Chua S Jr. Obesity, metabolic syndrome, and prostate cancer. Am J Clin Nutr. 2007; 86:843.
23. Gaston KE, Kim D, Singh S, et al. Racial differences in androgen receptor protein expression in men with clinically localized prostate cancer. J Urol. 2003; 170:990. [PubMed: 12913756]

24. Wallace TA, Prueitt RL, Yi M, et al. Tumor immunobiological differences in prostate cancer between African American and European American men. Cancer Res. 2008; 68:927. [PubMed: 18245496]

25. Rebbeck TR, Jaffe JM, Walker AH, et al. Modification of clinical presentation of prostate tumors by a novel genetic variant in CYP3A4. J Natl Cancer Inst. 1998; 90:1225. [PubMed: 9719084]

26. Powell IP, Zhou J, Sun Y, et al. CYP3A4 genetic variant and disease-free survival among white and black men after radical prostatectomy. J Urol. 2004; 72:1848. [PubMed: 15540736]

27. Bonilla C, Hernandez W, Kittles R, et al. CYP3A gene cluster, population stratification, and prostate cancer risk. J Urol. 2009; 181(suppl):818. abstract 2258.

28. Haiman CA, Patterson N, Freedman ML, et al. Multiple regions within 8q24 independently affect risk for prostate cancer. Nat Genet. 2007; 39:638. [PubMed: 17401364]

29. Robbins C, Torres JB, Hooker S, et al. Confirmation study of prostate cancer risk variants at 8q24 in African Americans identifies a novel risk locus. Genome Res. 2007; 17:1717. [PubMed: 17978284]

30. Helfand BT, Loeb S, Cashy J, et al. Tumor characteristics of carriers of the decode 8q24 prostate cancer susceptibility alleles. J Urol. 2008; 179:2197. [PubMed: 18423739]

Table 1

Latent PCa autopsy study

	No. Specimens		% Latent PCa		Mean Tumor Vol (cc)		% Gleason Score 6 or Less	
Age Group	**AAM**	**EAM**	**AAM**	**EAM**	**AAM**	**EAM**	**AAM**	**EAM**
20–29	156	30	8	11	0.031	0.091	100	100
30–39	130	76	31	31	0.091	0.089	99	100
40–49	178	130	43	38	0.436	0.215	97	100
50–59	111	103	46	44	0.941	0.899	87	93
60–69	34	54	72	68	0.875	2.555	86	87
70–79	21	33	77	69	0.562	2.941	65	84

Table 2

HG PIN autopsy study

	No. Specimens		% HGPIN	
Age Group	**AAM**	**EAM**	**AAM**	**EAM**
20–29	156	30	7	8
30–39	130	76	26	23
40–49	178	130	46	29
50–59	111	103	72	49
60–69	34	54	75	53
70–79	21	33	91	67

Table 3

RP

	No. Specimens		Mean Tumor Vol (cc)	
Age Group	**AAM**	**EAM**	**AAM**	**EAM**
30–39	1	1	5.59	4.08
40–49	57	53	3.11	2.54
50–59	258	321	4.24	3.82
60–69	416	438	5.09	4.56
70–79	86	91	5.18	6.2

Table 4

Age specific distant PCa incidence rates in metropolitan Detroit, 1995 to 2004

Age at Diagnosis	EAM Rate*	AAM Rate*	Rate Ratio
40–49	0.60	2.93	4.91
50–59	3.87	15.76	4.09
60–69	16.88	60.35	3.58
70–79	38.78	119.57	3.08

* Per 100,000 men ($p < 0.0001$).