IGF1 $(CA)_{19}$ Repeat and *IGFBP3* -202 A/C Genotypes and the Risk of Prostate Cancer in Black and White Men

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Abstract

We investigated the relationship between the insulin-like growth factor-1 (*IGF1*) cytosine-adenine repeat $(CA)_{19}$ polymorphism located upstream of the gene's transcription start site, the insulin-like growth factor binding protein-3 (*IGFBP3*) −202 A/C promoter region polymorphism, and prostate cancer risk in Black and White men. Study subjects were U.S. veterans ages 41 to 75 years identified at the Durham Veterans Administration Medical Center over a 2.5-year period. Controls (n = 93) were frequency matched to cases (n = 100) based on race (Black or White) and age. Multivariable unconditional logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI) for the associations between the polymorphisms and prostate cancer risk. For Blacks and Whites combined, an inverse association between prostate cancer and being homozygous for the most common *IGF1* repeat allele, $(CA)_{19}$, (adjusted OR, 0.3; 95% CI, 0.1-0.7) was observed. Similar associations were noted for both Blacks (OR, 0.2; 95% CI, 0.0-0.8) and Whites (OR, 0.4; 95% CI, 0.1-1.6) separately. No statistically significant associations between the *IGFBP3* C allele and prostate cancer were noted for Blacks (adjusted OR, 2.3; 95% CI, 0.8-6.2) or Whites (OR, 1.0; 95% CI, 0.3-3.1). The prevalence of the homozygous *IGF1* $(CA)_{19}$ genotype was much lower in Black controls (21%) than White controls (46%), which may, in part, explain the increased prostate cancer incidence in Black versus White men. Further research is needed to confirm these findings. (Cancer Epidemiol Biomarkers Prev 2005;14(2):403–8)

Introduction

Approximately 230,110 men in the United States are expected to develop prostate cancer during 2004, making it the most commonly diagnosed cancer among American men (1). In the United States, Blacks have higher rates of prostate cancer than Whites, with this difference most pronounced for undifferentiated tumors (2). Incidence rates of prostate cancer in the South are only slightly higher than national incidence rates. However, a clear discrepancy exists between national mortality rates and those in the southeast, with notably higher rates among southern Blacks (3).

Only a few prostate cancer risk factors have been consistently identified, including age, race, and family history (4). However, a growing body of evidence suggests that serum insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3) levels may play a role in prostate cancer risk and/or severity (5, 6). Previous findings relating circulating levels of IGF-1 and IGFBP-3 to prostate cancer risk and severity have been intriguing, although not entirely consistent (5-24). Of note, a positive association between increased IGF-1 levels and prostate cancer was found in three prospective studies (12-14). Three reports have shown an association between low serum IGF-1 levels and the most common allele, $(CA)_{19}$, of the polymorphic microsatellite CA repeat located 1 kb upstream from the *IGF1* transcription start site (25, 26, 32), although a third study did not confirm the relationship (5, 27). Recently, Rietveld et al. reported that homozygous carriers of the *IGF1* $(CA)_{19}$ repeat allele had an age-related decline in circulating IGF-1 levels; however, the same associations were not observed among heterozygotes and noncarriers of the common allele (26).

Two prospective studies (12, 13) reported that high circulating levels of IGFBP-3 were associated with a decreased risk of prostate cancer, whereas in a third prospective study (14), an overall positive association was reported. In two prospective studies, mean IGFBP-3 serum levels were significantly higher among subjects homozygous for the A allele than among those homozygous for the C allele of the single nucleotide A/C polymorphism at position −202 in the promoter region of the *IGFBP3* gene (30, 31). Carrying the C allele of the polymorphism was positively associated with advanced stage prostate cancer when compared with early stage in a study of Japanese men (28), with highest risk associated with carrying two C alleles. However, this study found no association between the polymorphism and risk of developing prostate cancer.

To our knowledge, there are no published studies examining the association between prostate cancer and polymorphisms in the *IGF1* gene. Additionally, we know of no studies that specifically explore Black/White differences in polymorphisms in the *IGF1* and *IGFBP3* genes and how those differences might be associated with prostate cancer risk. In this report, we examine the relationship between prostate cancer and the *IGF1* $(CA)_{19}$ repeat allele and the −202 A/C polymorphism in the promoter region of

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Table 1. Descriptive characteristics for DVAMC prostate cancer study cases and controls, overall and by race

Characteristic	Overall				P^*
	Cases (n = 100)		Controls (n = 93)		
	n (%)	Mean (SD)	n (%)	Mean (SD)	
Age at diagnosis/age at interview (y)	100	62.7 (7.4)	93	63.0 (7.6)	0.78
Height (in.)	98	69.4 (2.6)	89	69.5 (3.1)	0.94
Body mass index (kg/m^2)	98	27.8 (4.6)	89	28.7 (5.5)	0.22
Race					
White	50 (50.0)		44 (47.3)		0.71
Black	50 (50.0)		49 (52.7)		
Family history of prostate cancer in a father or a brother					
Yes	17 (17.4)		10 (11.0)		0.21
No	81 (82.7)		81 (89.0)		
Missing	2		2		
High school graduate					
Yes	85 (86.7)		73 (80.2)		0.23
No	13 (13.3)		18 (19.8)		
Missing	2		2		
Ever smoked 100 cigarettes					
Yes	79 (80.6)		72 (79.1)		0.80
No	19 (19.4)		19 (20.9)		
Missing	2		2		
Ever had diabetes					
Yes	27 (27.6)		39 (42.9)		0.03
No	71 (72.5)		52 (57.1)		
Missing	2		2		
Staging data					
Pathology only	7 (7.0)		NA		NA
Clinical only	68 (68.0)				
Pathology and clinical	25 (25.0)				

NOTE: χ^2 test for association between cases and controls unless otherwise noted.
*t Test for differences between cases and controls.

IGFBP3 among Black and White prostate cancer cases and controls enrolled in a hospital-based, case-control study conducted at the Durham Veterans Administration Medical Center (DVAMC) in Durham, NC.

Materials and Methods

Study Subjects. Data collection for this prostate cancer case-control study was conducted from January 1999 through July 2001. Newly diagnosed prostate cancer cases (n = 105) and controls (n = 96) were identified at the DVAMC. All subjects were between 41 to 75 years of age (at diagnosis for cases or time of interview for controls). All study subjects were English-speaking veterans who had no prior history of cancer (other than non-melanoma skin cancer) and were mentally and physically able to participate and be interviewed.

Prostate Cancer Cases. We identified newly diagnosed prostate cancer cases by searching DVAMC electronic surgical pathology records for *Systematized Nomenclature of Medicine* prostate topographical code (prefix 77) in combination with carcinoma morphologic code (suffix 3). In addition, we identified incident prostate cancer cases referred to the DVAMC for radiation therapy through abstraction of medical records in the radiation-oncology clinic. A stratified, simple random sampling procedure was employed, with prostate cancer cases selected on the basis of race (Black or White) and age at diagnosis (40-64 and 65-75 years old) to create four age-race strata with ~25% of the cases in each strata. Pathology reports were reviewed to verify case status. Once physician permission to contact the patient was obtained, an invitation letter to participate in the study was mailed and followed by an initial telephone screening call to verify eligibility. Prepaid postcards for study refusal were enclosed in the mailing. Cases were initially contacted within 9 months of diagnosis. A total of 105 prostate cancer cases enrolled in the study. The response rate among eligible prostate cancer cases was 70%. Among those who did not enroll in the study, 40 refused, 2 withdrew from the study, and 2 were lost to follow-up. Four of the 105 prostate cancer cases were diagnosed with distant disease, whereas the remaining either had localized or regional disease. For the current analysis, only those with local or regional disease, based on clinical stage or, when available, pathologic stage, were included. Prostate cancer cases, for which *IGF1* and *IGFBP3* genotypes could not be determined were excluded leaving 100 prostate cancer cases for the current analysis.

Control Subject Identification. Controls were frequency matched to the cases based on 5-year age groups and race (White or Black). A list of potential controls was generated by searching computer-generated DVAMC primary care clinic appointment lists for subjects in the appropriate age and race groups. The first 20 names were selected from the randomly sorted list, and the nurse/interviewer researched each of those 20 to verify race and to determine cancer history, address, and telephone number. A letter of invitation was then sent to the first six potentially eligible matches on the list. Subjects not refusing participation were called in the order they appeared on the list by a telephone interviewer who further explained the study and obtained verbal consent to conduct a brief telephone survey to confirm contact information and eligibility and to schedule an in-person interview. Once a control match

Table 1. Descriptive characteristics for DVAMC prostate cancer study cases and controls, overall and by race (Cont'd)

Blacks				*P**	Whites				*P**
Cases (*n* = 50)		Controls (*n* = 49)			Cases (*n* = 50)		Controls (*n* = 44)		
n (%)	Mean (SD)	*n* (%)	Mean (SD)		*n* (%)	Mean (SD)	*n* (%)	Mean (SD)	
50	61.2 (8.6)	49	61.8 (8.8)	0.75	50	64.3 (5.6)	44	64.5 (5.7)	0.87
49	69.9 (2.7)	47	69.6 (3.2)	0.84	49	69.3 (2.6)	42	69.5 (3.0)	0.75
49	28.4 (5.2)	47	28.8 (5.9)	0.70	49	27.2 (4.0)	42	28.6 (5.1)	0.16
0		0		NA	50 (100.0)		44 (100.0)		NA
50 (100.0)		49 (100.0)			0		0		
9 (18.0)		6 (12.8)		0.48	8 (16.7)		4 (9.1)		0.28
41 (82.0)		41 (87.2)			40 (83.3)		40 (90.9)		
		2			2				
45 (90.0)		40 (85.1)		0.46	40 (83.3)		33 (75.0)		0.32
5 (10.0)		7 (14.9)			8 (16.7)		11 (25.0)		
		2			2				
36 (72.0)		34 (72.3)		0.97	43 (89.6)		38 (86.4)		0.63
14 (28.0)		13 (27.7)			5 (10.4)		6 (13.6)		
		2			2				
14 (28.0)		23 (48.9)		0.03	13 (27.1)		16 (36.4)		0.34
36 (72.0)		24 (51.1)			35 (72.9)		28 (63.6)		
		2			2				
5 (10.0)		NA		NA	2 (4.0)		NA		NA
35 (70.0)					33 (66.0)				
10 (20.0)					15 (30.0)				

was enrolled, no other potential control subjects were contacted. Among nonrespondents, ~81 refused to participate, 2 withdrew from the study, and 2 were lost to follow-up. Altogether, 96 control subjects were enrolled. The response rate among eligible control subjects was 53%. Three control subjects for whom genotypes for *IGF1* and *IGFBP3* could not be determined were excluded from the current analysis leaving a total of 93 control subjects.

Subject Interviews. One in-person and two telephone interviews were conducted for each subject enrolled using a standardized questionnaire. Once eligibility was determined, in-person interviews were scheduled in conjunction with the patient's scheduled appointment at the DVAMC. In rare cases, when a subject was not returning to the DVAMC, a nurse/interviewer scheduled a home visit. During the face-to-face interview, the nurse/interviewer collected data related to occupational and residential history, as well as dietary data. In addition, a 30-mL blood sample was drawn and anthropometric data were collected. The two subsequent telephone interviews were conducted to obtain additional data including family history, sunlight exposure, prostate cancer screening history, and treatment information. A US$30.00 incentive was provided for both cases and controls upon completion of the interviews and blood draw.

Biospecimens and Laboratory Analyses

Blood Processing. Two 10-mL EDTA-treated tubes of blood were obtained at the time of the in-person interview. Whole blood samples were processed within 2 hours of collection and the buffy coat was isolated and placed in cryovials. All samples were stored at −70°C. DNA was extracted using the PureGene system of reagents (Gentra, Minneapolis, MN) according to the manufacturer's instructions. Isolated DNA was resuspended in hydration buffer and concentrations determined by absorbance at 260 and 280 nm.

IGF1 Polymorphism Analysis. PCR was done on extracted DNA using the forward primer 5′-GCTAGCCAGCTGGTGTTATT-3′ and reverse primer 5′-ACCACTCTGGGAGAAGGGTA-3′. For sequencing, the forward and reverse primers were unlabeled and obtained from Integrated DNA Technologies (Coralville, IA). These primers amplify the polymorphic cytosine-adenine $(CA)_n$ repeat 1 kb upstream of the human *IGF1* gene. The reaction was carried out in 15 μL (genotyping) or 50 μL (sequencing) volumes that contained 0.5 ng/μL of genomic DNA obtained from peripheral WBC, 0.5 nmol/L forward primer, 0.5 nmol/L reverse primer, 0.2 mmol/L deoxynucleotide triphosphate, 1.5 mmol/L $MgCl_2$ (Life Technologies, Gaithersburg, MD), 1× Gibco PCR buffer, and 0.025 units/μL Taq DNA polymerase (Life Technologies). PCR conditions consisted of an initial denaturing step at 95°C for 3 minutes, 30 cycles of 94°C for 45 seconds, 57°C for 45 seconds, and 72°C for 1 minute, an extension step at 72°C for 10 minutes, then at 4°C until analyzed. For microsatellite length genotyping, the forward primer was 5′-labeled with either 6-Fam, Hex, or NED (Applied Biosystems, Foster City, CA). Multiplexed samples were loaded in an ABI 3100 and allele analysis was done with Genotyper 2.1 software (Perkin-Elmer, Wellesley, MA). The size of the PCR products was determined in comparison with the internal ROX 400-size standard (Perkin-Elmer). For sequencing, completed PCR amplifications were purified using QIAquick 96 vacuum filter plates (Qiagen, Germantown, MD) and isolated in 150 μL of elution buffer. A sequencing reaction was done using 1 μL purified product and 4.4 pmol unlabeled forward primer in a BigDye Terminator Cycle Sequencing Reaction as described by the supplier (Applied Biosystems). The resulting samples

were run on 6.5% polyacrylamide gel in the ABI 377 and sequence determined with Genescan (Perkin-Elmer) software. In conducting these assays, the 188-bp repeat allele emerged as the most common allele. Given that the 192-bp allele has been reported to be the most common allele in most literature, we verified by DNA sequencing that this predominant allele contained $(CA)_{19}$ as previously described (29). Thus, our sizing of this allele at 188 bp as compared with the 192 bp in some reports likely reflects differences in electrophoresis conditions and software analysis.

IGFBP3 Polymorphism Analysis. The single nucleotide polymorphism in the promoter region of the *IGFBP3* gene located at -202 A/C was analyzed according to the method described by Jernstrom et al. (25). Briefly, 30 ng of genomic DNA were amplified with the following primers: sense 5′-CCACGAGGTACACACGAATG-3′ and antisense 5′-AGCCG-CAGTGCTCGCATCTGG-3′. Amplification conditions were as follows: using Platinum Taq polymerase (Invitrogen, Carlsbad, CA), a hot start for 10 minutes at 95°C was followed by 35 cycles of 96°C for 30 seconds, 64°C for 30 seconds, and 72°C for 1 minute with a final extension for 5 minutes at 72°C. The PCR products were then directly digested with the restriction endonuclease *Alw21I* (Fermentas, Hanover, MD) overnight at 37°C in the supplied buffer according to the manufacturer's recommendation. The digested products were then electrophoresed on 2% agarose gels bands visualized by ethidium bromide staining. Allele calls were made based upon the presence of the polymorphic *Alw21I* site. Because the 459-bp PCR product contains two additional *Alw21I* sites that are not polymorphic, this provided an unequivocal internal control for the enzyme digestion. The following allele calls were made: AA, 242 and 162 bp (the presence of the small internal fragment of 30 bp was not routinely detectable); CC, 288 and 162 bp; AC, 288, 242, and 162 bp.

Statistical Analyses. Most statistical analyses were done for Blacks and Whites combined and stratified by race. We tested descriptive continuous variables [age, body mass index (kg/m^2), and height] and categorical variables, including race (White/Black), family history of prostate cancer in father or brother (yes/no), ever diagnosed with diabetes (yes/no), high school graduate (yes/no), and ever smoked 100 cigarettes (yes/no) for case-control differences using the *t* test for continuous and the χ^2 test for categorical variables. *IGF1* CA repeat allele frequencies and genotype frequencies for homozygotes and heterozygotes for the most common allele, $(CA)_{19}$, were calculated for cases and controls. We tested *IGF1* and *IGFBP3* genotype frequencies in controls for deviation from Hardy-Weinberg equilibrium using the χ^2 test.

Unconditional multivariable logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI) for the association between prostate cancer and *IGF1* CA repeat genotypes [$(CA)_{19}/(CA)_{19}$, $(CA)_{19}$/x, and x/x (reference) where x/x = any repeat allele other than $(CA)_{19}$)]. Similarly, unconditional multivariable logistic regression was used to model the association between prostate cancer and *IGFBP3* genotypes [CC, AC, and AA (reference)] at the -202 position in the promoter region. Potential confounders, including age, race, education, height, body mass index, family history of prostate cancer, smoking history, and history of diabetes, that changed the OR for the association between prostate cancer and any of the genotypes by ≥10% were included in the final multivariable logistic regression model. An additional logistic regression model was computed that included both the *IGF1* genotype variables and the *IGFBP3* genotype variables simultaneously along with the other potential cofounders. Although typically our case-control matching strategy would suggest the use of conditional rather than unconditional logistic regression, such an analysis would have resulted in a substantial loss of data as we were unable to complete all pairs, and among those that were completed, loss of genotype information for one or the other of a pair resulted in unusable pairs and power loss. A comparison of conditional and unconditional results for an identical subset of completed pairs (62 pairs for IGF1 analyses, 70 pairs for IGFBP3 analyses) yielded very similar results; we therefore applied the unconditional method to the overall data set to increase power. In race-specific models, race was not included as a covariate. All analyses were conducted using SAS version 8.2 (Statistical Analysis Software, Cary, NC). All reported tests were two tailed.

Table 2. Frequencies of *IGF1* CA repeat alleles and genotypes and *IGFBP3* −202 A/C genotypes in DVAMC prostate cancer cases and controls

	Overall		Blacks		Whites	
	Cases, *n* = 100 (%)	Controls, *n* = 93 (%)	Cases, *n* = 50 (%)	Controls, *n* = 49 (%)	Cases, *n* = 50 (%)	Controls, *n* = 44 (%)
IGF1 CA repeat allele frequencies*						
$(CA)_{11}$	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
$(CA)_{16}$	2 (1.0)	9 (5.4)	2 (2.1)	9 (10.5)	0 (0.0)	0 (0.0)
$(CA)_{17}$	8 (4.1)	5 (3.0)	5 (5.2)	3 (3.5)	3 (3.1)	2 (2.4)
$(CA)_{18}$	39 (20.1)	23 (13.7)	34 (35.4)	17 (19.8)	5 (5.1)	6 (7.3)
$(CA)_{19}$	84 (43.3)	91 (54.2)	27 (28.1)	36 (41.9)	57 (58.2)	55 (67.1)
$(CA)_{20}$	41 (21.1)	24 (14.3)	14 (14.6)	10 (11.6)	27 (27.6)	14 (17.1)
$(CA)_{21}$	15 (7.7)	12 (7.1)	12 (12.5)	9 (10.5)	3 (3.1)	3 (3.7)
$(CA)_{22}$	3 (1.6)	2 (1.2)	0 (0.0)	1 (1.2)	3 (3.1)	1 (1.2)
$(CA)_{24}$	2 (1.0)	1 (0.6)	2 (2.1)	1 (1.2)	0 (0.0)	0 (0.0)
Missing	6	18	4	12	2	6
IGF1 CA repeat genotype						
$(CA)_{19}/(CA)_{19}$	22 (22.7)	28 (33.3)	4 (8.3)	9 (20.9)	18 (36.7)	19 (46.3)
$(CA)_{19}$/x	40 (41.2)	35 (41.7)	19 (39.6)	18 (41.9)	21 (42.9)	17 (41.5)
x/x	35 (36.1)	21 (25.0)	25 (52.1)	16 (37.2)	10 (20.4)	5 (12.2)
Missing	3	9	2	6	1	3
IGFBP3 genotype						
AA	18 (18.0)	23 (25.0)	9 (18.0)	15 (31.3)	9 (18.0)	8 (18.2)
AC	55 (55.0)	41 (44.6)	30 (60.0)	21 (43.8)	25 (50.0)	20 (45.5)
CC	27 (27.0)	28 (30.4)	11 (22.0)	12 (25.0)	16 (32.0)	16 (36.4)
Missing		1		1		

NOTE: x, non-$(CA)_{19}$ repeat allele.
**n* is for alleles (two/person) rather than subjects.

Table 3. Adjusted ORs and 95% CIs for associations between *IGF1* $(CA)_{19}$ repeat and *IGFBP3* −202 A/C genotypes in DVAMC prostate cancer cases and controls

	Overall*		Blacks*		Whites*	
	No. cases/no. controls	OR† (95% CI)	No. cases/no. controls	OR† (95% CI)	No. cases/no. controls	OR† (95% CI)
IGF1 $(CA)_{19}$ genotypes‡						
$(CA)_{19}/(CA)_{19}$	20/28	0.3 (0.1-0.7)	3/9	0.2 (0.0-0.8)	17/19	0.4 (0.1-1.6)
$(CA)_{19}$/x	39/33	0.6 (0.3-1.4)	19/17	0.7 (0.3-1.7)	20/16	0.7 (0.2-2.4)
x/x	35/20	1.0 (reference)	25/15	1.0 (reference)	10/5	1.0 (reference)
IGFBP3 -202 A/C genotypes						
CC	26/26	1.3 (0.6-3.1)	11/11	1.5 (0.4-5.1)	15/15	1.0 (0.3-3.5)
AC	53/39	1.9 (0.9-4.1)	29/20	2.9 (1.0-8.6)	24/19	1.0 (0.3-3.3)
AA	18/23	1.0 (reference)	9/15	1.0 (reference)	9/8	1.0 (reference)
IGFBP3 -202 A/C genotypes						
CC/AC	79/65	1.7 (0.8-3.4)	40/31	2.3 (0.8-6.2)	39/34	1.0 (0.3-3.1)
AA	18/23	1.0 (reference)	9/15	1.0 (reference)	9/8	1.0 (reference)

*Frequencies exclude subjects with missing values for any of the adjustment variables.
†OR adjusted for age, body mass index, height, and diabetes (also race in the overall analyses).
‡x, non-$(CA)_{19}$ allele.

Results

Characteristics of cases and controls are reported in Table 1 for Blacks and Whites combined and separately by race. The mean age of the Black cases and controls was ~3 years younger than that of the White cases and controls. By design, about half of the cases and controls were Black and half were White. The mean age for both cases and controls was 64 years. Slightly more cases (17%) than controls (11%) reported a family history of prostate cancer in a father or a brother. This case-control difference was more pronounced among Whites than among Blacks. Over 80% of the cases and controls had at least a high school education. More controls than cases reported having been diagnosed with diabetes.

IGF1 CA Repeat and IGFBP3 -202 A/C Genotype Analyses. Frequency distributions for the *IGF1* CA repeat alleles and *IGFBP3* promoter polymorphism for prostate cancer cases and controls are presented in Table 2. Genotype frequencies among controls did not deviate from the assumption of Hardy-Weinberg equilibrium for either *IGF1* ($P = 0.14$) or *IGFBP3* ($P = 0.31$). The most common allele was the IGF1 $(CA)_{19}$ repeat allele with a frequency of 43% of in prostate cancer cases and 54% in controls. When stratifying on race, the $(CA)_{19}$ allele was the most common allele among Black and White controls; however, the prevalence of the $(CA)_{19}$ allele among Blacks (42%) was much lower than among Whites (67%; $P = 0.001$). Associations between prostate cancer and polymorphisms in *IGF1* are found in Table 3. An inverse association between prostate cancer and being homozygous for the $(CA)_{19}$ repeat allele (adjusted OR, 0.3; 95% CI, 0.1-0.7) was found. There was a suggestion of an allele ''dose effect'' among those who were heterozygous for $(CA)_{19}$ (adjusted OR, 0.6; 95% CI, 0.3-1.4). Similar associations were found for both races when analyzed separately.

With regard to *IGFBP3*, overall, 27% of cases and 30% of controls were homozygous for the C allele at the -202 A/C locus, whereas 18% of cases and 25% of controls carried no C allele (Table 2). Blacks had a lower percentage of C homozygotes in both cases (22%) and controls (25%) than did Whites (32% and 36%, respectively). Associations between prostate cancer and the -202 A/C polymorphism in the promoter region of the *IGFBP3* gene are reported in Table 3. The point estimate for the association between prostate cancer and carrying a C allele in Blacks (OR, 2.3; 95% CI, 0.8-6.2), although not statistically significant, was higher than the point estimate for this association in Whites (OR, 1.0; 95% CI, 0.3-3.1).

Finally, we did a logistic regression analysis that included both the *IGF1* and *IGFBP3* genotypes and found negligible differences in the associations between each of these genes and prostate cancer compared with the associations found in analyses of each gene separately (data not shown).

Discussion

The results of this case-control analysis support a relationship between the common *IGF1* repeat allele and a decreased risk of prostate cancer in both Blacks and Whites. We did not find any evidence that this relationship could be explained by potential confounders. Previous studies have found high IGF-1 serum levels are associated with an increased risk of developing prostate cancer (12-14). There is recent evidence that genetic factors may contribute to the observed variation in IGF-1 in sera. Several reports have found an association between lower serum or plasma levels of IGF-1 and the most common allele (192 bp or 19 repeats) compared with other polymorphic variants (5, 26, 27). To our knowledge, this is the first published study to examine the relationship between polymorphisms in the *IGF1* gene and prostate cancer risk. The adjusted OR suggests an overall 70% reduction in risk for carriers of the $(CA)_{19}$ repeat allele.

We also examined the relationship between a promoter polymorphism in *IGFBP3* and found no statistically significant relationship with prostate cancer. However, among Blacks, but not among Whites, there was some suggestion of an increased risk associated with the C allele. Our data show that the White and Black cases have similar C allele frequencies. However, the frequency of the C allele in our data is lower among the Black controls compared with the White controls. Therefore, the difference in the association with the C allele in Blacks versus Whites resulted from the different C allele frequencies in the controls. This relationship warrants further investigation in a large study. Consistent with our finding of no association between the *IGFBP3* polymorphism and prostate cancer are the findings from two studies that suggest that only 6% to 8% of interindividual variability in circulating IGFBP-3 serum levels may be explained by the *IGFBP3* polymorphism we examined in this study (30, 31). Therefore, it is likely that variations in other genes as well as other environmental factors may play a bigger role in the variation of serum IGFBP-3 levels than the *IGFBP3* −202 A/C genotype.

A major finding of this study is that the most common allele in the *IGF1* gene, the $(CA)_{19}$ repeat, was found to be associated with a decreased risk of prostate cancer. This finding has particular implications for risk of prostate cancer among Blacks because the prevalence of the homozygote genotype for this allele is much lower among Blacks (21%) than among Whites (46%). Our results suggest the differences in the prevalence of the protective common *IGF1* allele may, in part, explain discrepancies in the incidence and mortality of prostate cancer in Blacks versus Whites. To our knowledge, there are no published studies examining the association between polymorphisms in *IGF1* and prostate cancer risk. Additionally, our data do not support that a polymorphism in the promoter region of *IGFBP3* plays an important role in prostate cancer risk. Given that our data represent a small, hospital-based, case-control study and a sample comprised exclusively of veterans, there is a need to replicate these results in a larger, more generalizable population. Due to the small sample size, we were not able to examine these relationships by age or stage at diagnosis. Furthermore, our understanding of how IGF peptides interact is not complete and additional research is needed to more thoroughly understand the relationship between IGF peptides and the risk of prostate cancer across racial groups.

This report provides estimates of the association between genetic polymorphisms in *IGF1*, *IGFBP3*, and prostate cancer risk among Black and White men and supports an important role of genetic variation in the occurrence of prostate cancer. Further research of additional genetic factors on the IGF pathway and investigation of gene × environment interactions is needed.

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