Prostate Cancer Risk in Relation to Insulin-like Growth Factor (IGF)-I and IGF-Binding Protein-3: A Prospective Multiethnic Study

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Introduction

Despite its importance (1, 2), relatively little is known about prostate cancer etiology (3, 4). Risks are highest among North American Blacks and lowest in Asians, whereas Whites seem to lie in between (5). Levels of insulin-like growth factor (IGF)-I have been associated with increased risk of prostate cancer (6-10), but other well-designed studies have reported null results (11-13). Studies of IGF-binding protein-3 (IGFBP-3) have reported both increased (12) and decreased risk of prostate cancer (8, 13) as well as no association (9-11). Inconsistent results suggest additional factors, including but not limited to methodologic differences, unmeasured confounding variables, and differences in ethnic diversity of populations. Our purpose was to determine the associations between prediagnostic levels of IGF-I and IGFBP-3 and risk of prostate cancer, and our multiethnic population provided the opportunity to explore the role ethnicity might play.

Materials and Methods

As part of the original case-control study (14-17), from 1990 to 1992, healthy male controls were matched to cases by age, region, and ethnicity. Participants were asked to fast for 12 h before blood specimen collection, and to the extent possible, specimens were collected early in the morning. Of the 1,121 specimens (40 mL of venous blood), adequate sample remained on 1,012 subjects. Outcome ascertainment was conducted by linkage to state and provincial cancer registries and vital statistics data in California (United States), Hawaii (United States), and British Columbia (Canada). Prostate cancer occurred 1 or more years after blood draw in 96 men with enough sera for analysis. Men known to be alive and free of prostate cancer when the case was diagnosed were matched by ethnicity (White, Black, Chinese, and Japanese), region (Los Angeles, San Francisco, Hawaii, and Vancouver), and 5-year age category in a ratio of four controls per case (n = 416). Ethical approval was given by the University of British Columbia Research Ethics Board.

For each subject, a 1.0-mL vial of serum was removed from storage, packed in dry ice, and shipped to the laboratory of one of us (M.D.P.) at the Lady Davis Institute for Medical Research (Montreal, Quebec, Canada). Laboratory staff used ELISA (Diagnostic Systems Laboratories, Inc.) to analyze samples, blinded to ethnicity and case-control status. Samples were assayed twice, and the mean was used for analysis.

Spearman correlation coefficients were used to examine relationships between serum measurements and potential confounders [age at blood draw; waist circumference; weight; Quetelet's index (kg/m^2) or body mass index; daily dietary intake of calories, protein, carbohydrates, fat, calcium, vitamin D, and alcohol; daily hours sitting or in vigorous activity; serum levels of C-peptide, sex hormone–binding globulin, prostate-specific antigen, cholesterol, total testosterone, percentage free testosterone, and dihydrotestosterone; and family history of prostate cancer]. The change-in-estimate criterion was used to select confounders with a 5% change in the estimate of the main variable. Analysis of risk was carried out using standard case-control methods (18) and Statistical Package for the Social Sciences version 11 software (SPSS, Inc.). Odds ratios (OR) were calculated using multivariate logistic regression. Interactions with main variables were examined by entering the interaction term into the logistic regression model. The study had 80% power to detect a relative risk of $\geq$2.54 for highest versus lowest quartile (α = 0.05, two sided).

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Table 1. Characteristics of prostate cancer cases and controls by ethnic group

	Blacks		Whites		Asians	
	Cases (n = 29)	Controls (n = 124)	Cases (n = 34)	Controls (n = 150)	Cases (n = 33)	Controls (n = 142)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age (y)*	67.1 (6.1)	67.1 (7.8)	68.7 (6.8)	69.7 (8.2)	71.2 (4.6)	69.5 (7.1)
Waist (cm)*	93.9 (9.9)	98.2 (12.5)	96.2 (8.6)	98.6 (10.7)	87.0 (8.2)	87.5 (7.4)
BMI (kg/m^{-2})*	25.9 (4.0)	28.0 (4.4)	26.0 (3.3)	26.9 (3.9)	24.1 (3.0)	24.3 (3.0)
Analyte levels						
IGF-I (ng/mL)	236 (75)	228 (74)	240 (84)	228 (86)	231 (80)	226 (86)
IGFBP-3 (ng/mL)	3,725 (651)	3,688 (808)	4,027 (896)	3,911 (907)	3,670 (665)	3,772 (859)
IGF-to-IGFBP-3 ratio	6.3 (1.5)	6.2 (1.6)	6.0 (1.4)	6.0 (1.6)	6.3 (1.7)	5.9 (1.5)

NOTE: Excludes those diagnosed in the 1st year after enrollment. Asian group is Chinese and Japanese groups combined.
Abbreviation: BMI, body mass index.
*At enrollment.

Results

Data by ethnic group show that cases and controls were similar for variables that might influence a relationship between IGFs and prostate cancer (Table 1). In Blacks, body mass index at enrollment was lower in cases than controls (P = 0.04). There were no statistically significant case-control differences in IGF-I levels or IGFBP-3 levels for any ethnic group or between ethnic groups.

Prediagnostic IGFBP-3 levels were positively associated with prostate cancer risk only among Black men (Table 2). Comparing with the first or lowest quartile, ORs were elevated in the second quartile [OR, 3.28; 95% confidence interval (95% CI), 0.85-12.68] and third quartile (OR, 5.52; 95% CI, 1.39-21.86) of IGFBP-3 but not in the fourth (highest) quartile. The interaction between IGFBP-3 levels and ethnicity was not statistically significant. No association was observed for levels of IGF-I or IGF-to-IGFBP-3 ratio and prostate cancer risk. Mutual adjustment of IGF-I and IGFBP-3 did not alter our results nor did adjustment for other potential confounders.

Discussion

We observed no association of prostate cancer risk with prediagnostic IGF-I. We observed a positive association with prediagnostic IGFBP-3 and prostate cancer but only for the subgroup of Black men and only in the third quartile. Furthermore, this observation was not supported by the test for interaction between ethnicity and IGFBP-3 levels and may therefore be due to chance.

Levels of IGF-I may increase risk of some common cancers (19, 20), but results with respect to prostate cancer have been inconsistent, with some prospective studies reporting null associations similar to ours (11-13). Levels of IGF-I during adolescence or early adulthood may be more etiologically relevant than levels at a single point later in life. A prospective study conducted in northern Sweden reported increased risk associated with IGF-I levels only among younger men (diagnosed at age <59 years; ref. 7), but in our study population, this group makes up <9% of the total. Although differing associations of body mass index with IGFs among ethnic groups

Table 2. Age-adjusted ORs and 95% CIs for prostate cancer risk in relation to prediagnostic IGF-I, IGFBP-3, and IGF-to-IGFBP-3 ratio

	All (N = 512)		Blacks (n = 153)		Whites (n = 184)		Asians (n = 175)	
	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)
IGF-I								
Quartile 1*	126	1.00	35	1.00	43	1.00	48	1.00
Quartile 2	129	1.15 (0.61-2.18)	37	0.48 (0.13-1.84)	48	1.97 (0.66-5.86)	44	1.14 (0.40-3.21)
Quartile 3	126	1.02 (0.53-1.98)	44	1.17 (0.39-3.53)	47	1.17 (0.36-3.77)	35	0.65 (0.18-2.36)
Quartile 4	131	1.26 (0.66-2.41)	37	1.09 (0.34-3.49)	46	1.16 (0.35-3.83)	48	1.65 (0.58-4.71)
IGFBP-3								
Quartile 1 †	120	1.00	37	1.00	40	1.00	43	1.00
Quartile 2	140	2.28 (1.19-4.38)	54	3.28 (0.85-12.68)	37	2.02 (0.64-6.37)	49	2.05 (0.74-5.70)
Quartile 3	127	1.46 (0.73-2.95)	37	5.52 (1.39-21.86)	45	0.39 (0.09-1.70)	45	1.20 (0.39-3.69)
Quartile 4	125	1.35 (0.15-6.59)	25	1.01 (0.15-6.59)	62	1.70 (0.57-5.07)	38	0.69 (0.18-2.63)
IGF-to-IGFBP-3 ratio								
Quartile 1 ‡	127	1.00	33	1.00	54	1.00	40	1.00
Quartile 2	120	0.80 (0.41-1.58)	28	0.53 (0.12-2.38)	46	0.28 (0.07-1.06)	46	2.19 (0.72-6.62)
Quartile 3	123	0.89 (0.46-1.72)	40	1.31 (0.41-4.14)	37	0.91 (0.32-2.63)	46	0.64 (0.16-2.52)
Quartile 4	138	1.52 (0.83-2.79)	52	1.12 (0.39-3.63)	45	1.41 (0.55-3.61)	41	2.67 (0.83-8.60)

NOTE: Excludes those diagnosed in the 1st year after enrollment. Asian group is Chinese and Japanese groups combined.
*Quartiles among control subjects used as the cutoffs. First (lowest) quartile is reference category. Cut points are as follows (all in ng/mL): quartile 1, <174.05; quartile 2, 174.05 to 219.76; quartile 3, 219.77 to 272.36; and quartile 4, >272.36.
† Quartiles among control subjects used as the cutoffs. First (lowest) quartile is reference category. Cut points are as follows (all in ng/mL): quartile 1, <3,209.20; quartile 2, 3,209.20 to 3,776.54; quartile 3, 3,776.55 to 4,382.98; and quartile 4, >4,382.98.
‡ Quartiles among control subjects used as the cutoffs. First (lowest) quartile is reference category. Cut points are as follows (all in ng/mL): quartile 1, <4.94; quartile 2, 4.94 to 5.68; quartile 3, 5.69 to 6.85; and quartile 4, >6.85.

may affect results (21), in our population no clear patterns were observed.

Although we did not observe differences in the risk relationships associated with ethnicity, caution is required in interpretation due to small numbers for subgroup analyses. It is also not clear whether circulating concentrations of IGFs reflect tissue concentrations or biological activity. We recognize that levels of growth factors may be important with respect to prognosis for aggressive prostate cancer, but we did not have data to address that question. Our results are strengthened by the prospectively collected samples and the linkages to ascertain death and cancer incidence data. To address possible occult disease, we conducted analyses that excluded those diagnosed in the first 1 or 2 years after enrollment.

In conclusion, we did not observe an association of prediagnostic IGF-I or IGFBP-3 with risk of developing prostate cancer.

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