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Introduction

Components of metabolic syndrome, including elevated serum insulin and C-peptide levels, seem to affect risk of developing prostate cancer, but inconsistently. Recently, an inverse association was reported in a prospective U.S. study (1), whereas a prospective Norwegian study reported the opposite result that metabolic syndrome predicted prostate cancer (2). We therefore wanted to examine the question, and we investigated the association of prediagnostic C-peptide and risk of developing prostate cancer in a U.S. and Canadian cohort, which was multiethnic and would allow us to explore possible effects of ethnicity on the findings.

Materials and Methods

In 1990 to 1992, we collected blood samples from 760 men who had served as controls in three study centers [San Francisco (United States), Hawaii (United States), and Vancouver (Canada)] of a multiethnic case-control study of prostate cancer (3). We followed these men for prostate cancer occurrence from study enrollment until 2003. Prostate cancer occurred 1 or more years after blood draw in 58 of the men with enough sera for analysis. Men known to be alive and free of prostate cancer at the time the case was diagnosed were matched to each case on age, ethnicity (Black, White, Chinese, and Japanese), and area of residence in a ratio of about four controls for each case. One case was excluded due to an extremely high C-peptide value, leaving 57 cases and 243 controls. 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).

For each subject, a single 1.0-mL vial of serum was removed from storage in California or Hawaii, 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 and were blinded to subject ethnicity, study center, and disease status.

We used SPSS version 11 statistical software (4) for logistic regression analysis, adjusting for age at blood draw. C-peptide values were log transformed to approximate a normal distribution. The study had 80% power to detect a relative risk of 2.88 or greater for the highest versus the lowest tertile, with an $\alpha = 0.05$, two sided. Tests for interactions were done for age, weight, height, body mass index, waist circumference, study center, ethnicity, and levels of testosterone, free testosterone, percentage free testosterone, and sex hormone–binding globulin.

Results

Prediagnostic levels of C-peptide were similar in cases (mean, 2.22 ng/mL; SD, 1.69) and controls (mean, 2.12 ng/mL; SD, 1.42), although levels did vary by ethnic group, with the highest levels (mean, 2.79 ng/mL; SD, 2.12) in White cases (Table 1). In univariate and age-adjusted analyses, for both continuous and categorical variables, C-peptide was not associated with risk of developing prostate cancer in any ethnic group or in the whole group combined. C-peptide was more strongly negatively correlated with androgens (testosterone and dihydrotestosterone) and sex hormone–binding globulin in cases than in controls (data not shown), although tests for interaction were not statistically significant, and adjustment for these and other variables (e.g., time since last meal, body mass index, waist circumference, caloric intake, and dietary vitamin D intake) did not alter results.

Discussion

We saw no association between C-peptide and risk of prostate cancer. This result supports neither the inverse association reported by Tande et al. (1) nor the positive

Table 1. C-peptide levels (nanogram per milliliter) by race and disease status, with odds ratios and 95% confidence intervals

	Cases		Controls		*P*, *t* test	OR (95% CI)*
	n	Mean (SD)	*n*	Mean (SD)		
All groups	57	2.22 (1.69)	243	2.12 (1.42)	0.18	1.12 (0.59-2.29)
Black	13	1.67 (0.87)	58	2.03 (1.48)	0.41	0.80 (0.16-3.87)
White	19	2.79 (2.12)	78	2.38 (1.42)	0.32	1.15 (0.34-3.90)
Chinese	9	2.50 (2.25)	42	2.42 (1.85)	0.91	1.04 (0.19-5.60)
Japanese	16	1.83 (1.07)	63	1.66 (0.80)	0.47	1.82 (0.47-7.12)
Asian†						1.37 (0.49-3.86)

NOTE: Excludes all those diagnosed in the 1st year after enrollment.
Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval.
*Highest tertile compared with lowest (reference) tertile, age adjusted.
†Chinese and Japanese groups combined.

association reported by Lund Haheim (2), both of which were based on more than one component of metabolic syndrome. Our data are consistent with an earlier prospective study in the Northern Sweden Health and Disease Cohort where prostate cancer was not associated with levels of insulin (5). Although we measured C-peptide instead of insulin, C-peptide and predictors of C-peptide have been examined in place of insulin in studies of other cancers (6, 7). Very few studies have reported on direct measurements of C-peptide and risk of prostate cancer. A recent larger and more comprehensive study of insulin resistance and prostate cancer in the Northern Sweden Health and Disease Cohort reported an inverse association of C-peptide and nonaggressive prostate cancer in men less than 59 years of age at blood sampling but not among older men such as those in our cohort where the mean age at blood sampling was 69 years (8). We recognize that although we and others have not found a strong relationship with risk of prostate cancer, C-peptide or other indicators of insulin resistance may be negative prognostic markers among men with prostate cancer. In a nested case-control study within the Physicians' Health Study, prediagnostic C-peptide levels were not associated with risk of incident prostate cancer but were positively associated with prostate cancer mortality, specifically among overweight men (9).

Although we had the statistical power to detect an association similar to that observed in a case-control study of prostate cancer risk and insulin resistance among Chinese (odds ratio, 2.78; 95% confidence interval, 1.63-4.72), we saw no association (10). This may be due to the fact that our subgroup of Chinese subjects was small or to methodologic differences such as sampling serum prospectively before the onset of disease. We did not observe an interaction with low levels of vitamin D as in a recent Finnish study (11), but we based our analysis on dietary intake data, which due to homeostasis may not be well correlated with serum levels. We minimized information bias through comprehensive case ascertainment.

In summary, our data do not support C-peptide as a predictor of prostate cancer.

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