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Cancer Epidemiology, Biomarkers & Prevention

Null Results in Brief

No Association of Plasma Levels of Adiponectin and c-peptide with Risk of Aggressive Prostate Cancer in the Cancer Prevention Study II Nutrition Cohort

Victoria L. Stevens, Eric J. Jacobs, Juzhong Sun, and Susan M. Gapstur

Abstract

Background: Obesity is associated with a higher risk of aggressive prostate cancer and alters circulating levels of insulin and adiponectin, two hormones that influence biologic processes implicated in carcinogenesis. Results of some studies showed associations of circulating levels of adiponectin, insulin, and c-peptide (a marker of insulin secretion) with aggressive prostate cancer, but the size of these studies was limited.

Methods: A nested case–control study of 272 aggressive prostate cancer cases [Gleason score ≥7 (4+3) or T3-T4] and 272 age- and race-matched controls from the Cancer Prevention Study II Nutrition Cohort was conducted to determine the associations of prediagnostic plasma levels of c-peptide and adiponectin with risk of aggressive prostate cancer.

Results: Neither circulating adiponectin nor c-peptide was associated with risk of aggressive prostate cancer. In analyses of the highest-risk aggressive prostate cancer (Gleason score ≥8 or T3-T4), the highest quartile of c-peptide, compared with the lowest, was associated with an OR of 1.41 [95% confidence interval (CI), 0.72–2.78].

Conclusions: Our findings provide no support for the hypothesis that adiponectin is associated with risk of aggressive prostate cancer but a possible association of high levels of c-peptide with particularly high-risk prostate cancer cannot be ruled out.

Impact: These results indicate that changes in circulating levels of adiponectin and c-peptide do not play an important role in risk of aggressive prostate cancer. *Cancer Epidemiol Biomarkers Prev; 23(5); 890–2. ©2014 AACR.*

Introduction

Obesity is associated with a lower risk of localized prostate cancer and higher risk of aggressive and fatal cancer (1). Adiponectin (2) and insulin (3) are hormones whose circulating levels are influenced by obesity and may play a role in carcinogenesis. The association of adiponectin with prostate cancer was investigated by two prospective studies (4, 5), which yielded conflicting results. Whereas Li and colleagues (4) reported a significant inverse association of adiponectin with both high grade and lethal prostate cancer, Touvier and colleagues (5) found no significant association with prostate cancer overall. As summarized in a recent review of diabetes and prostate cancer (6), several studies have found inconsistent results for the association of insulin or c-peptide, a marker of insulin secretion, with prostate cancer risk. We examined associations of plasma adiponectin and c-peptide levels with aggressive prostate cancer in a nested case–control study within the Cancer Prevention Study II (CPS-II) Nutrition Cohort. With 272 cases, this is the largest study of these circulating markers and risk of aggressive prostate cancer.

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Materials and Methods

Study population

Men in this analysis were from the 86,404 male participants in the CPS-II Nutrition Cohort, a prospective study of cancer incidence begun in 1992. Details of the recruitment and characteristics of this cohort have been described previously (7). Incident cancers were self-reported on follow-up questionnaires sent to participants in 1997 and every 2 years thereafter, and were verified through medical records or state cancer registries. Additional cancers were ascertained through linkage to the National Death Index. Blood samples were collected on a subset of cohort participants (17,411 men) between 1998 and 2001 and were stored in liquid nitrogen vapor phase.

We identified 272 men who were diagnosed with aggressive prostate cancer after providing a blood sample,

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before June 30, 2007, and had no history of cancer (except nonmelanoma skin cancer) before their prostate cancer diagnosis. Aggressive prostate cancer was defined as Gleason score ≥7 (4+3) and/or stage T3 or T4 at diagnosis, or ultimately fatal prostate cancer of unknown stage and grade at diagnosis ($N = 2$). For each case, one control, matched on date of birth (±6 months), date of blood collection (±6 months), and race/ethnicity, was randomly selected from men with no history of cancer on the diagnosis date of the case.

Laboratory procedures

Plasma adiponectin and c-peptide levels were measured in the laboratory of Dr. Michael Pollak (McGill University, Montreal, Canada) using commercially available ELISA assays. Samples were analyzed in batches of 37, which included three quality control replicates. Coefficients of variation and intraclass correlation coefficients based on these replicates were 6.5% and 97.3% for adiponectin and 7.2% and 98.3% for c-peptide.

Statistical analyses

Quartiles of adiponectin and c-peptide levels were defined on the basis of their distribution among controls. The association of each analyte with prostate cancer risk was determined using conditional logistic regression to generate ORs and 95% confidence intervals (CI). All models were adjusted for body mass index, family history of prostate cancer, physical activity, total calcium intake, and energy intake. Adjustment for education, alcohol intake, smoking, history of diabetes, and aspirin use did not alter the risk estimates and therefore these factors were not included in multivariate-adjusted models. Adjustment of adiponectin levels for c-peptide levels and *vice versa* also did not alter risk estimates.

Results

The aggressive prostate cancer cases and controls in this study were similar with respect to age and race because of matching (Table 1). Aggressive prostate cancer cases were less likely to report a history of ever having had a prostate-specific antigen (PSA) test on the 1997 follow-up survey (before blood draw), although most of the cases and controls reported some history of PSA testing. Cases were more likely than controls to report a family history of prostate cancer.

Adiponectin and c-peptide were not associated with all aggressive prostate cancer in multivariate-adjusted models (Table 2). For adiponectin, results were similar when the cases were further restricted to high-risk prostate cancer (Gleason score ≥8 and/or tumor extent T3-T4) as defined by the National Comprehensive Cancer Network guidelines (ref. 8; Table 2). For c-peptide, the highest quartile, compared with the lowest, was associated with an elevated, albeit not significant, risk of high-risk prostate cancer (OR, 1.41; 95% CI, 0.72–2.78). Excluding subjects diagnosed within 2 years of blood draw did not substantially change the associations (data not shown).

Table 1. Characteristics of the prostate cancer cases and matched controls from the CPS-II Nutrition Cohort

Variable	Controls ($N = 272$) *N* (%)	Cases ($N = 272$) *N* (%)
Age at blood draw		
≤65	51 (18.7)	50 (18.3)
66–70	90 (33.1)	90 (33.1)
71–75	77 (28.3)	81 (29.8)
76+	54 (19.9)	51 (18.8)
Race		
White	271 (99.6)	271 (99.6)
Black	1 (0.4)	1 (0.4)
Family history of prostate cancer[a]		
Yes	31 (11.4)	50 (18.4)
Diabetes[b]		
Yes	33 (12.1)	27 (9.9)
BMI (kg/m^2)[b]		
<25	112 (41.2)	101 (37.1)
25–<30	108 (39.7)	128 (47.1)
30+	47 (17.3)	41 (15.1)
Missing	5 (1.8)	2 (0.7)
Physical activity (METs/wk)[a]		
<7	76 (27.9)	75 (27.6)
7–<17.5	108 (39.7)	112 (41.2)
17.5–<24.5	38 (14.0)	48 (17.7)
24.5+	48 (17.7)	34 (12.5)
Missing	2 (0.7)	3 (1.1)
History of PSA testing[a]		
Never	24 (8.8)	40 (14.7)
Within 2 years	192 (70.6)	180 (66.2)
>2 years	30 (11.0)	28 (10.3)
Unknown	26 (9.6)	24 (8.8)
Gleason score		
6 or 7 (3+4)		27 (9.9)
7 (4+3)		108 (39.7)
8		73 (26.8)
9–10		46 (16.9)
Unknown		18 (6.6)
Stage[c]		
T2 (organ confined)		194 (71.3)
T3		44 (16.2)
T4		25 (9.2)
Unknown		9 (3.3)

Abbreviations: BMI, body mass index; METs, metabolic equivalents.

[a]As reported on 1997 questionnaire.

[b]As reported at time of blood draw (1998–2001).

[c]Unknown category includes six cases defined as regional using SEER summary stage that corresponds to stage T3 or T4.

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Table 2. Association of adiponectin and c-peptide levels with prostate cancer in CPS-II

	All aggressive[a]			High risk[b]		
Analyte	**Cases**	**Controls**	**OR (95% CI)**	**Cases**	**Controls**	**OR (95% CI)**
Adiponectin (ng/mL)						
<6,178	62	68	1.00 (ref)	43	38	1.00 (ref)
6,178–<7,879	61	68	1.05 (0.62–1.78)	38	43	0.76 (0.38–1.52)
7,879–<11,109	86	68	1.43 (0.87–2.36)	55	43	1.10 (0.58–2.11)
≥11,109	63	68	1.11 (0.64–1.93)	36	48	0.70 (0.33–1.49)
P trend			0.59			0.56
c-peptide (ng/mL)						
<2.95	72	68	1.00 (ref)	43	47	1.00 (ref)
2.95–<4.69	59	68	0.69 (0.42–1.16)	34	41	0.94 (0.48–1.82)
4.69–<6.55	60	68	0.77 (0.47–1.28)	39	42	0.95 (0.48–1.87)
≥6.55	80	67	1.18 (0.69–2.02)	55	41	1.41 (0.72–2.78)
P trend			0.44			0.31

NOTE: Model stratified on pairs and adjusted for family history of prostate cancer, body mass index, physical activity in metabolic equivalents (METs), total calcium intake, and energy intake.

[a]Gleason score ≥7 (4+3) or T3 or T4 or death from prostate cancer.

[b]Gleason score ≥8 or stage T3 or T4.

Discussion

This study included 272 aggressive prostate cancer cases, more than any previous study c-peptide or adiponectin levels (1, 2). Despite the comparatively large sample size, we found no evidence that differences in prediagnostic levels of adiponectin were associated with risk of aggressive prostate cancer. However, we cannot preclude the possibility that high levels of c-peptide may be associated with the highest-risk aggressive prostate cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: V.L. Stevens, E.J. Jacobs

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): E.J. Jacobs, S.M. Gapstur

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): V.L. Stevens, E.J. Jacobs, J. Sun

Writing, review, and/or revision of the manuscript: V.L. Stevens, E.J. Jacobs, J. Sun, S.M. Gapstur

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