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Finasteride modifies the relation between serum C-peptide and prostate cancer risk: results from the Prostate Cancer Prevention Trial

Marian L. Neuhouser[1,*], **Cathee Till**[1], **Alan Kristal**[1,2], **Phyllis Goodman**[1], **Ashraful Hoque**[3], **Elizabeth A. Platz**[4], **Ann W. Hsing**[5], **Demetrius Albanes**[5], **Howard L. Parnes**[6], and **Michael Pollak**[7]

[1]Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA 98109-1024

[2]Department of Epidemiology, School of Public Health, University of Washington, Seattle, WA 98195

[3]Department of Clinical Cancer Prevention, The University of Texas M.D. Anderson Cancer Center, Houston, TX 77030

[4]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205

[5]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892

[6]Prostate and Urologic Cancer Research Group, Division of Cancer Prevention, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892

[7]Departments of Medicine and Oncology, McGill University, Montreal, Canada H3A 2T5

Abstract

BACKGROUND—Hyperinsulinemia and obesity-related metabolic disturbances are common and have been associated with increased cancer risk and poor prognosis.

METHODS—Data are from a case-control study within the Prostate Cancer Prevention Trial (PCPT), a randomized, placebo-controlled trial testing finasteride vs. placebo for primary prevention of prostate cancer. Cases (n=1803) and controls (n= 1797) were matched on age, PCPT treatment arm, and family history of prostate cancer; controls included all eligible non-whites. Outcomes were biopsy-determined. Baseline bloods were assayed for serum C-peptide (marker of insulin secretion) and leptin (an adipokine) using ELISA. Logistic regression calculated odds ratios for total prostate cancer and polytomous logistic regression calculated odds ratios for low-grade (Gleason < 7) and high-grade (Gleason ≥ 7) disease. Results were stratified by treatment arm for C-peptide.

RESULTS—For men on placebo, higher vs. lower serum C-peptide was associated with a near two-fold increased risk of high-grade prostate cancer (Gleason ≥ 7) (multivariate-adjusted OR= 1.88, 95%CI 1.19-2.97, p trend = 0.004). When C-peptide was modeled as a continuous variable, every unit increase in [log(C-peptide)], resulted in a 39% increased risk of high-grade disease (p=0.01). In contrast, there was no significant relationship between C-peptide and high-grade

*Corresponding Author: Division of Public Health Sciences Fred Hutchinson Cancer Research Center 1100 Fairview Avenue North, M4-B402 Seattle, WA 98109-1024 Tel: 206-667-4797 Fax; 206-667-7850 mneuhous@fhcrc.org.

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prostate cancer among men receiving finasteride. Leptin was not independently associated with high-grade prostate cancer.

CONCLUSIONS—These results support findings from other observational studies that high serum C-peptide and insulin-resistance, but not leptin, are associated with increased risk of high-grade prostate cancer. Our novel finding is that the C-peptide-associated risk was attenuated by use of finasteride.

Keywords

prostate neoplasms; finasteride; obesity; insulin; insulin resistance; C-peptide; leptin

INTRODUCTION

Metabolic dysfunction is a recognized risk factor for carcinogenesis, including carcinogenesis of the prostate (1-3). Important examples of metabolic dysfunction include hyperinsulinemia and insulin resistance (1, 2). These clinical characteristics are of particular interest since insulin-activated signaling involves pathways known to be involved in carcinogenesis (4-7).

Several biologically plausible mechanisms may underlie the role of insulin in carcinogenesis. For example, insulin promotes cell division; thus, a metabolic milieu of hypersinsulinemia is likely to promote cellular proliferation and hyperplasia (8-10). Alternatively, insulin may facilitate carcinogenesis by favoring cell survival and inhibiting apoptosis through effects on AKT and MTOR (11, 12), allowing accumulation of genetic damage.

Increasing evidence suggests that obesity is a strong risk factor and/or adverse prognostic factor for cancer, including prostate cancer (13, 14). While the mechanism for the obesity-prostate cancer association is not definitively identified, one possibility is that obesity-related hyperinsulinemia could lead to inappropriate survival and proliferation of insulin-receptor positive at-risk and/or transformed prostate epithelial cells (8, 10, 15-17). Consistent with this view, plasma levels of C-peptide, which serve as a marker of insulin secretion, increase with obesity (8, 18, 19), and higher levels are associated with increased risk of prostate-cancer specific mortality (7). Other evidence suggests that insulin may influence cancer risk through effects on inflammation, oxidative stress or sex hormones (5). Regardless of the mechanism, targeting the insulin axis for cancer prevention is attractive since insulin axis components are modifiable by diet, weight loss, physical activity and pharmacological approaches (20-22).

Biomarkers of metabolic dysfunction and insulin resistance include glucose, insulin, C-peptide, glycosylated hemoglobin and calculated measures, such as HOMA (homeostasis model of assessment) (23). Of these, C-peptide has been used as the biomarker of insulin secretion in many population-based studies (7). Proinsulin is synthesized by the pancreas and cleaved into insulin and C-peptide prior to release in the circulation. In non-fasting samples, C-peptide is considered a more reliable marker of insulin secretion since, compared to insulin, it has a longer half-life and is metabolically stable (7, 24).

Three investigations have examined these biomarkers, excess glucose, insulin and insulin resistance, in relation to risk of breast and colorectal cancers (25-27), but relatively few studies have investigated insulin resistance or C-peptide with prostate cancer risk. A Swedish cohort study reported an inverse association of high vs. low plasma C-peptide with overall prostate cancer risk. However, a non-significant increased risk of aggressive disease (defined as Gleason ≥ 8, lymph node metastasis, PSA > 50, bone metastasis or prostate

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cancer death) was observed in the cohort (28). More recently, the Physicians' Health Study showed that men diagnosed with prostate cancer who had higher vs. lower baseline C-peptide had a more than two-fold risk of dying from their prostate cancer. These results became somewhat attenuated after controlling for BMI and clinical characteristics such as Gleason grade and stage (7). Further subgroup analysis revealed that overweight men who also had elevated C-peptide had a four-fold increased risk of death from prostate cancer (7). A recent nested case-control study (n=100 prostate cancer cases/400 controls) reported OR = 2.55 (95% CI 1.18-5.51, p, trend = 0.02) for the fourth vs. first quartile of serum insulin (29). In contrast, a multi-ethnic study of 114 prostate cancer cases and 484 controls reported no association of prediagnostic C-peptide with prostate cancer risk (30).

An alternative and equally plausible pathway by which obesity may increase prostate cancer risk is via adipokines. Adipose tissue synthesizes these peptides (or adipokines) such as leptin and adiponectin, and the more adipose tissue the greater the synthesis of these peptides (31, 32). Leptin was originally identified as a satiety signal, but other functions were subsequently identified, including involvement in glucose and fatty acid oxidation, complex orchestrating of the hormonal control of food intake, regulation of other hormones (i.e., growth hormone, reproductive hormones) and a role in the promotion of mitogenic activity (31, 32). In addition, *in vitro* studies have suggested that leptin inhibits apoptosis and promotes cell proliferation in prostate cancer cells (33-35), rendering it a potential mediator of the relationship between obesity and cancer risk.

Finding effective measures for prostate cancer prevention are important clinical and public health priorities, particularly for high-grade disease that typically has a poor prognosis. Therefore, we sought to better understand both of these potential mechanisms (insulin secretion/insulin resistance and leptin) in relation to prostate cancer risk in the Prostate Cancer Prevention Trial.

MATERIALS AND METHODS

Study Design and Study Population

The Prostate Cancer Prevention Trial (PCPT) was a randomized, placebo-controlled trial testing whether the 5α-reductase inhibitor, finasteride, could reduce the 7-year period prevalence of prostate cancer. Details regarding study design and participant characteristics have been described previously (36). Briefly, at 221 clinical centers across the United States 18,880 men aged 55 years and older with a normal digital rectal exam (DRE) and prostate-specific antigen (PSA) level ≤ 3.0 ng/ml, as well as no history of prostate cancer, severe benign prostatic hyperplasia, or clinically significant co-morbid conditions that would have precluded successful completion of the study protocol, were randomized to receive finasteride (5 mg/day) or placebo. During the course of the PCPT, men underwent annual DRE and PSA measures and a prostate biopsy was recommended for all men with an abnormal DRE or a finasteride-adjusted PSA of ≥ 4.0 ng/ml (37). At the final study visit, all men without a previous diagnosis of prostate cancer were offered an end-of-study biopsy. Biopsies were collected under transrectal ultrasonographic guidance and a minimum of six biopsy specimens (cores) were collected from each participant. All biopsies were reviewed both by a local study pathologist and a central study pathologist (38, 39). Discordant pathology interpretations were arbitrated by a referee pathologist and concordance was achieved in all cases (36, 38, 39). Pathologists were blinded to the randomization arm of all participants. Tumors were graded with the Gleason system by central pathology review at the Prostate Diagnostic Laboratory (Denver, CO). Low-grade prostate cancer included tumors with Gleason score <7 and high-grade tumors were those with Gleason score ≥ 7 (36). Study procedures were approved by Institutional Review Boards at each of the participating clinical centers, the Southwest Oncology Group (SWOG, San Antonio, TX)

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and the SWOG Data and Statistical Center (Fred Hutchinson Cancer Research Center, Seattle, WA). All men signed informed consent. An independent data safety and monitoring committee met every six months throughout the course of the trial to review data on safety, adherence and diagnosis of prostate cancer (36).

This report presents data from a nested-case control study in the PCPT. Cases were men with biopsy-determined prostate cancer identified either during an interim or end-of-study biopsy and who had baseline serum available for analysis (n=1803). We retained the low and high-grade classifications as used in the original trial report for these analyses (low grade = Gleason < 7; high grade = Gleason ≥ 7) (36). Controls were selected from men who completed the end-of-study biopsy procedure, had no evidence of prostate cancer and had archived baseline serum samples (n=1797). Controls were frequency matched to cases on distributions of age (in 5-year age groups), PCPT treatment arm (finasteride vs. placebo) and positive family history for first degree relative with prostate cancer; controls were oversampled to include all non-whites.

Data Collection

Blood Collection and Processing—Nonfasting blood specimens were collected at screening (approximately three months prior to randomization) and yearly thereafter. Venous blood was drawn into collection tubes without anticoagulant, refrigerated and shipped via overnight courier to the PCPT specimen repository where they were centrifuged, aliquoted and stored at −70°C until analysis (40).

Laboratory Analysis—Serum C-peptide and leptin concentrations were assayed with a standard ELISA using a single production lot of reagents (Diagnostic Systems Limited, Webster, TX). All assays were conducted in duplicate and the mean of the duplicate measures are reported. Two sets of QC samples (from pooled specimens) were included for quality control and the coefficients of variation (CVs) from these QC pools were 5.6% and 3.8% for the C-peptide assays and 4.9% and 4.5% for the leptin assays. Laboratory technicians were blinded to both the randomization assignment and case-control status of all participants.

Other Data—Demographic, personal medical history, family history of prostate cancer and lifestyle habits, such as smoking, alcohol and physical activity habits were collected by self-report at baseline; the measurement characteristics of many of these self-assessment tools are published (41-43). Height and weight were assessed at the baseline clinic visit using a standard protocol (44) and weight was assessed annually thereafter. Body mass index (BMI) was calculated as [weight(kg)/height(m^2)] and standard clinical cutpoints categorized BMI as normal = BMI < 25.0; overweight = BMI 25.0 to < 30.0; and obese = BMI ≥ 30.0 (45). Circumferences of the abdomen, waist, hip and thigh were measured at 1-year post randomization (46). As the body circumference measurements were voluntary, some clinical centers did not participate, resulting in missing data for [n=348 (10%)] of the participants.

Statistical Analysis—The control group was oversampled with minorities to include all control-eligible non-whites. Thus, baseline demographic and lifestyle characteristics were adjusted for race (white vs. non-white) using linear regression to calculate least squares means for continuous variables and adjusted percents for categorical variables.

Serum concentrations of C-peptide and leptin were categorized into quartiles based on the distribution in the controls. Logistic regression was used to calculate odds ratios and 95% confidence intervals for risk of total prostate cancer and polytomous logistic regression was used to calculate odds ratios and 95% confidence intervals of both low-grade and high-grade

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prostate cancer. The polytomous regression with a generalized logit link permits a model including both low-grade and high-grade cancers as outcomes in the same model, contrasted with no cancer. Model covariates were carefully selected based on *a priori* information about potential confounding as well as diagnostic procedures completed as part of our modeling exercises. Final covariates included age, race (white/non-white), family history of first-degree relative with prostate cancer, insulin use at baseline, BMI and smoking (pack-years of smoking). Since this nested case-control study was part of a randomized, controlled trial, we had an *a priori* hypothesis that there may be effect modification of the active agent in the trial, finasteride, on C-peptide or leptin in relation to prostate cancer risk. We also hypothesized that there could be effect modification by measures of adiposity (e.g., BMI, waist circumference), particularly for leptin since it is produced by adipocytes. Tests for multiplicative interaction were conducted by entering cross-product terms of C-peptide and finasteride or measures of adiposity and testing these terms with the Wald test. We conducted a mediating factors analysis with BMI and leptin to determine whether any observed BMI-prostate cancer risk associations were explained by leptin. All statistical tests are two-sided with $p<0.05$ considered statistically significant. SAS (version 9.0, Cary, NC) was used for all statistical analyses.

RESULTS

Cases and controls did not differ with respect to race-adjusted BMI, age, body circumferences, family history of prostate cancer, current smoking status or alcohol habits. Controls reported higher levels of physical activity than cases (10.6% vs. 8.2% were very active, p=0.02). Controls also had more total pack-years of smoking (p=0.02) and were more likely to report a diagnosis of diabetes or use insulin and other diabetes medications at baseline compared to cases (p=0.05) (Table 1).

Unadjusted baseline serum C-peptide concentrations did not differ between cases and controls (Table 2). To determine whether finasteride influenced serum C-peptide, we assayed the blood specimens of a random subset of participants (n=267) at both baseline and two years later. While mean concentrations of C-peptide increased for all men between baseline and year 2, there was no evidence that finasteride differentially affected these changes. Mean baseline-year 2 differences did not vary by treatment arm, even after adjustment for years since baseline blood draw and participant weight change from baseline to year 2 (data not shown).

Our initial modeling included the combined arms of the trial [intervention (finasteride) and placebo] and the interaction term between treatment arm and C-peptide. Notably, we observed a statistically significant interaction of C-peptide with treatment arm (p-interaction=0.04 for all cancers and p=0.03 for Gleason ≥ 7). Therefore, all remaining models were stratified by treatment arm. Additionally, since men with self-reported diabetes at baseline might have higher circulating C-peptide due to disease-associated poor glycemic control, we conducted additional analyses excluding diabetic men to determine whether they were driving the observed associations. However, as these analyses did not materially alter the results or their interpretation, men with diabetes at baseline were retained in the final model.

Table 3 gives results for multivariate-adjusted associations of serum C-peptide with prostate cancer risk, stratified by treatment arm. In the placebo arm, C-peptide was associated with modest increases in risk for total and low-grade disease (OR = 1.21, 95%CI 0.93-1.57, p trend = 0.11 for all cancers). Findings for high-grade disease were considerably stronger. For men in the placebo arm, those with higher baseline serum C-peptide concentrations had a nearly two-fold, statistically significant increased risk of high-grade prostate cancer,

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compared to men with lower baseline serum C-peptide (OR=1.88, 95% CI 1.19-2.97, p trend = 0.004). While the PCPT defined high-grade as Gleason ≥ 7, analyses where high-grade was restricted to Gleason ≥ 8 were equally strong, but cell sizes very small and confidence intervals very wide. Therefore, data presented are for Gleason < 7 and ≥ 7 only. We next examined C-peptide as a continuous variable. In analyses where C-peptide was modeled as [log(C-peptide)], associations with high-grade disease were strong. For every unit increase in [log(C-peptide)], men randomized to placebo had a 39% increased risk of high-grade prostate cancer (p<0.01).

In contrast to the C-peptide risk associations observed in the placebo arm, among men randomized to finasteride, there was no evidence for C-peptide-associated risk with either total prostate cancer, low-grade or high grade-disease, even for men with high serum C-peptide. For low-grade disease, there was a suggestion of lowered risk among finasteride users (OR for high vs. low C-peptide = 0.77, 95% CI, 0.54-1.09). However, for high-grade disease, prostate cancer risk estimates hovered around unity. Results were similar when high-grade was defined as Gleason ≥ 8. Likewise, when C-peptide was modeled as a continuous variable there was a modest suggestion of lowered risk for low-grade disease; for each unit increase of [log (C-peptide)] the odds ratio for prostate cancer was 0.87, 95% CI 0.72-1.05, p trend = 0.16. In the continuous model, no association was observed between C-peptide and high-grade prostate cancer for men taking finasteride. All results in Table 3 were repeated, restricting the sample to men who were black or non-Hispanic white (i.e., excluding all other race groups). The results and their interpretation did not differ from models where all race/ethnicities were included. We also found no differences in risk across race groups, albeit sample sizes were small (data not shown). Therefore, the final models as presented included all non-white and white men.

Adiposity strongly influences insulin-resistance and C-peptide. In this study sample, the correlations of BMI and waist circumference with serum C-peptide were r= 0.25 and r=0.27, respectively. To investigate whether these adiposity measures modified the association between C-peptide and prostate cancer risk, we modeled C-peptide with the following interaction terms in separate models: (1) BMI 25.0-29.9 (overweight), BMI ≥ 30.0 (obese); (2) elevated waist circumference (≥ 102 cm); (3) elevated waist:hip ratio (≥ 1.0); and (4) a category termed "very high risk of metabolic dysfunction" defined as BMI ≥ 30.0 + waist circumference ≥ 102 cm, or BMI ≥ 35.0 (45). We restricted these analyses to the placebo arm and we present high-grade disease only since this was the group with the elevated risk in the Table 3 models. The results in Table 4 are presented for low and high C-peptide (above and below the median concentration) and for each model the reference group is the lowest risk category (i.e., low C-peptide + normal BMI; or low C-peptide + waist-hip ratio < 1.0). We observed no evidence for effect modification of C-peptide by measures of adiposity.

We conducted several other exploratory analyses in an attempt to further understand why the C-peptide-high-grade disease association was observed only in the PCPT placebo arm. First, we examined whether results may have been biased by the fact that PCPT participants had end-of-study biopsies in addition to biopsies by indication throughout the trial. However, analyses stratified by end-of-study vs. for-cause biopsy and analyses stratified by year of diagnosis did not change the interpretation of results. Similarly, neither adjusting for time since blood draw, prostate volume, trends in PSA nor changes in participant weight over time altered the results or their interpretation (data not shown).

To fully understand the associations of obesity-related factors with prostate cancer risk, particularly high-grade disease, we next investigated whether serum leptin was associated with prostate cancer risk (Table 5). Specifically, we conducted a mediating factors analysis

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to understand whether leptin mediates the association of obesity with prostate cancer risk, as suggested by *in vitro* studies (33, 35). Our initial modeling did not demonstrate an interaction of finasteride with leptin, so for these models the intervention and placebo arms are combined. When BMI is modeled as the primary exposure, the odds ratio for high-grade prostate cancer among obese men is 1.39 (95%CI 1.03-1.87, p-trend = 0.03). Obesity was associated with a modest inverse association with low-grade disease (OR= 0.80, 95% CI 0.64-1.0, p-trend = 0.04). Leptin alone was likewise inversely associated with low-grade but not high-grade prostate cancer. In the mediating factors analysis, the BMI association with high-grade disease remains strong, even after including leptin in the model. Finally, we re-ran the C-peptide models again (from Table 3) but controlling for leptin. C-peptide continued to be associated with high-grade disease in the placebo arm (but not finasteride arm) even after controlling for leptin (OR = 1.99, 95% CI 1.24-3.19, p-trend < 0.001, data not shown). The association of obesity with high-grade prostate cancer risk does not appear to be mediated by leptin.

DISCUSSION

In the Prostate Cancer Prevention Trial, men in the placebo arm of the trial who had higher serum C-peptide had a nearly two-fold increased risk of high-grade prostate cancer, relative to men with lower serum C-peptide. The results suggest that metabolic abnormalities are associated with prostate cancer risk, but the mechanism appears to be through insulin resistance and not via adipokines, such as leptin. The C-peptide findings were independent of the principal risk factors for prostate cancer: age, race and family history of prostate cancer (47). The observed associations were also independent of adiposity measures, such as BMI and waist circumference, which recent reports suggest are important prostate cancer risk factors (14, 48, 49). For every unit increase in [log(C-peptide)] there was a 39% increased risk of high-grade prostate cancer. These findings are strengthened by the fact that all men underwent either interim (cases only) or end-of-study (cases and controls) biopsies in the PCPT (36). Thus, the control group is not contaminated with any pre-clinical cases, as may be the case with other studies.

In contrast, men taking finasteride had no apparent increased risk for high-grade prostate cancer, even for men with high serum C-peptide. The strength of the interaction of C-peptide with finasteride was somewhat unexpected. Finasteride inhibits 5α-reductase, which converts testosterone to the more potent and biologically active dihydrotestosterone (36, 50). We do not have evidence that finasteride affects C-peptide per se since analysis of the small subset (n=267) of specimens assayed for both baseline and year 2 serum C-peptide did not support a C-peptide reducing effect by finasteride. There is some evidence, though, that finasteride may indirectly affect metabolic function. Two previous reports demonstrated that finasteride slows weight gain trajectories (51, 52). If the finasteride-induced decreased weight gain slope affected some of the downstream events that are up-regulated by C-peptide (e.g., AKT, mTOR) (12, 17), then finasteride could essentially override C-peptide driven events without affecting C-peptide itself. Another possible explanation is that proliferation of neoplastic cells in the prostate may depend on both insulin and androgens. Since androgen levels (as DHT) are reduced among men on finasteride, neoplastic progression could be slowed despite high insulin levels. It is also possible that multiple mechanisms are at work. Investigations using methods developed for genetic epidemiology that simultaneously model metabolic and hormonal pathways, and finasteride's role in those pathways, may be a particularly useful approach to use in the future to understand these complex relationships (53-55). Regardless of the underlying biological mechanism, the evidence that men with higher serum C-peptide who used finasteride, but did not have an increased prostate cancer risk, may be clinically meaningful and should be investigated further.

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The results from the PCPT placebo arm are consistent with most, but not all previous studies of C-peptide and prostate cancer risk. The Physicians' Health Study (PHS) reported that risk of death from prostate cancer was over two-fold higher for men with higher vs. lower C-peptide (7). Unlike the PCPT, however, the PHS observed an interaction of BMI with C-peptide such that men in the highest C-peptide quartile who were also overweight (BMI > 25.0) had a four-fold increased risk of prostate cancer mortality, but those with high C-peptide who were not overweight had no increased risk of prostate cancer death (7). It is possible that the PCPT did not have sufficient variation in adiposity measures to detect an interaction effect with C-peptide as only 25% of the study sample was of normal BMI. Other studies have reported on insulin and insulin resistance measures, such as HOMA (homeostasis model of assessment). Two studies conducted in Chinese men support a positive association of insulin or insulin resistance with prostate cancer risk (5, 6), as does one recent study of Finnish men (29). In contrast to the positive reports for C-peptide and other measures of metabolic dysfunction, Borugian reported no association of serum C-peptide with prostate cancer risk, but the study was very small (n= 57 cases) and no results were reported by disease stage or Gleason grade (30).

Despite the increasing evidence in this and other reports that metabolic dysfunction increases prostate cancer risk (5, 7, 13, 48), one somewhat paradoxical observation still exists. Several observational studies have reported inverse associations of diabetes with prostate cancer risk (14, 56, 57). Because diabetes is a disease of disordered glucose metabolism, and often the consequence of obesity (18, 58), evidence suggesting that diabetes reduces prostate cancer risk is curious. Diabetic men also have altered sex hormone profiles as a consequence of their disease (59), which could possibly explain the relationship, but how these complex pathways weave together to affect disease risk is yet to be determined. A particularly complex piece of this clinical picture is the marked heterogeneity of diabetes. For example, many patients with type II diabetes initially have hyperinsulinemia, but in latter stages of the disease actually have hypoinsulinemia, a state that may further reduce androgens and potentially reduce prostate cancer risk (14, 60). Alternatively, the link between diabetes and decreased prostate cancer risk may relate to drugs used to treat diabetes rather than diabetes itself. Metformin is very commonly used in the treatment of type II diabetes (61), and metformin has recently been shown to have potent antiproliferative properties (62). These may relate not only to metformin-induced reduction in the hyperinsulinemia seen in type II diabetics, but also to direct mechanisms of growth inhibition related to metformin activation of the AMP-kinase signaling pathway (63-66). In addition, many diabetics routinely use statins due to co-morbid cardiovascular symptoms; statins have been noted to lower prostate cancer risk (67, 68). Future studies, rather than simply examining relationships between diabetes and prostate cancer, may provide more insight into mechanisms by exploring individually the specific relationships between risk and the levels of various hormones (including insulin), glucose, measures of obesity, and anti-diabetic drug use. Although not definitive, several recent studies have raised the question of increased cancer risk among diabetics who use insulin, in contrast to possibly reduced risk among those who use metformin (69, 70).

Our finding of no relationship of leptin to high-grade prostate cancer risk is a potentially important one, particularly with regard to formulating programs for prevention and control. Evidence to support an association of leptin with prostate cancer is inconsistent from observational studies. A Swedish case-control study reported a relative risk of 2.4 for high vs. low serum leptin in relation to prostate cancer risk (71). However, two subsequent case-control studies in China and Norway reported no statistically significant association of leptin with prostate cancer (6, 72). A more recent case-control study in Texas (USA) also reported no association of leptin with prostate cancer risk (73). However, the PCPT presented here are consistent with results from a study using the fatless A-ZIP/F-1 transgenic mouse model.

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These animals are insulin-resistant and are in a chronic state of inflammation, but they lack white adipose tissue and thus, have near undetectable levels of adipokines, such as leptin (74, 75). Nunuz et al reported that the A-ZIP/F-1 mice produced more skin and mammary tumors than wildtype mice (using a classical topical DMBA application for the skin cancers and breeding with C3(1)/T-Ag transgenic mice for the mammary cancers). The tumors developed in spite of very low levels of adipokines, but high levels of insulin and inflammatory factors and up-regulation of insulin-regulated signaling pathways involved in carcinogenesis. The authors and others conclude that the obesity-cancer association may be mediated by insulin resistance and inflammation, rather than adipokines (74, 75). Our results in the PCPT are similar; C-peptide was strongly associated with increased risk of prostate cancer and the effects remain strong after controlling for obesity-related factors. The relationships were attenuated by finasteride. Conversely, the association of obesity with prostate cancer risk was not mediated by leptin. Such findings quite likely have relevance for future programs of prostate cancer prevention and control wherein it might be most effective to improve measures of insulin sensitivity as a measure of prevention and control.

This study has several strengths. The PCPT was a large placebo-controlled randomized trial. The trial design specified that prostate cancer outcomes would be based on biopsy results. As such, the control group used in these analyses all had negative prostate biopsies, largely eliminating the possibility that controls may have had undiagnosed or undetected disease. Other strengths include the carefully collected data throughout the course of the trial, the central pathology laboratory for uniform adjudication of all cases (including adjudication of Gleason grade). Limitations should also be noted, including the fact that the PCPT included few minorities. While we oversampled non-white controls to increase power for analyses by race, the power for any race-specific subgroups was limited. Further, few deaths from prostate cancer have occurred in the PCPT so we are unable to conduct analyses to examine mortality as an endpoint.

In conclusion, these results from the PCPT suggest that men with elevated C-peptide have an increased risk of high-grade prostate cancer. The lack of support in the PCPT for an association of leptin with prostate cancer suggests that the obesity-cancer associations may be mediated by insulin-resistance rather than by adipose-derived factors, such as leptin. The findings reported here confirm and extend results from other cohorts (7). Because insulin-resistance type syndromes respond well to lifestyle and pharmacological treatments, consideration should be given to preventive interventions to lower insulin resistance as a means of prostate cancer prevention. Our finding that men with elevated C-peptide who also used finasteride had no increased prostate cancer risk is novel. Further research is needed to understand the clinical significance and mechanisms underlying the finasteride-C-peptide interaction presented in this report. We cannot rule out the possibility that C-peptide levels may be of use in defining a subpopulation of men for whom finasteride-based prevention programs would be particularly useful.

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Table 1

Race-Adjusted Baseline Demographic and Lifestyle Characteristics of the PCPT Participants (n=3600)[1]

	Prostate Cancer				*P* [2]
	Cases (n=1803)		**Controls (n=1797)**		
Race	**n**	**%**	**n**	**%**	
White	1674	92.8	1426	79.4	
Black	82	4.5	174	9.7	
Other	47	2.6	197	11.0	
	LS Mean	**95%CI**	**LS Mean**	**95%CI**	
Age (years)	63.6	63.3-63.8	63.7	63.4-63.9	0.58
Body Mass Index [wt(kg)/ht(m)^2]	27.5	27.3-27.7	27.6	27.4-27.8	0.42
Waist circumference (cm)	101.8	101.3-102.3	102.3	101.8-102.8	0.16
Waist:Hip ratio	0.96	0.95-0.96	0.96	0.96-0.96	0.70
Smoking (pack-years)	14.0	13.2-14.8	15.3	14.6-16.1	0.02
Alcohol intake (g/day)	9.7	9.0-10.4	9.2	8.5-9.9	0.28
	n	**% (adjusted)** [1]	**n**	**%(adjusted)** [1]	
Intervention arm[3]	761	43.0	763	41.7	0.42
Diabetes or insulin use	84	5.3	133	6.8	0.05
Family history of prostate cancer	384	20.8	382	21.8	0.48
Body Mass Index [wt(kg)/ht(m)^2]					
Normal (< 25.0)	498	27.7	447	25.3	0.11
Overweight (25.0-29.9)	913	50.8	941	53.2	0.15
Obese (≥ 30.0)	376	21.3	391	21.3	0.99
Physical activity					
Sedentary	309	17.6	313	17.1	0.68
Light activity	746	41.3	738	41.5	0.91
Moderate activity	592	32.9	550	30.8	0.20
Very active	149	8.2	188	10.6	0.02
Smoking status					
Never smoker	644	35.4	615	34.6	0.62
Current smoker	122	7.1	138	7.3	0.87
Past smoker	1037	57.5	1044	58.1	0.69
Education					
High school or less	308	17.6	348	18.9	0.32
Some college/college degree	490	27.7	542	29.7	0.20
Graduate/professional school	1004	54.7	906	51.4	0.05

[1]Least squares means and adjusted percents are adjusted for race (white vs. non-white) due to the inclusion of all non-whites in the control group (see methods section for details).

[2] p values are adjusted for race using linear regression to calculate least squaresd means, adjusted percents and p-values (see methods section for details).

[3] Intervention arm participants were randomized to finasteride.

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Table 2

Distributions of C-Peptide in the Prostate Cancer Prevention Trial

	Baseline Serum C-peptide (ng/ml)						
	n		**Mean**	**SD**	**25th% tile**	**50th %tile**	**75 %tile**
All participants	3600		3.64	2.32	1.86	3.08	4.88
Cases	1803		3.64	2.32	1.87	3.14	4.87
Controls	1797		3.63	2.33	1.84	3.03	4.90
	Baseline and Year 2 Serum C-Peptide (ng/ml) [1]						
	n	**Baseline Median**	**Baseline Mean**	**SD**	**Year 2 Median**	**Year 2 Mean**	**SD**
All Participants[1]	267	3.08	3.56	2.18	4.06	4.46	2.71
Cases							
All cases	127	3.32	3.84	2.25	4.32	4.78	2.77
Placebo	67	3.21	3.60	2.05	4.27	4.46	2.64
Finasteride	60	3.91	4.10	2.45	4.52	5.13	2.89
Controls							
All controls	140	2.78	3.32	2.08	3.58	4.14	2.62
Placebo	73	2.76	3.23	2.05	3.81	4.24	2.46
Finasteride	67	2.89	3.41	2.13	3.11	4.03	2.80

[1]Subset of randomly selected participants (n=267) had repeat measures.

Table 3

Associations of Serum C-peptide Concentrations with Prostate Cancer Risk by in the PCPT by treatment arm (placebo/finasteride)

	Quartile of serum C-peptide concentration (ng/ml)				
Placebo Arm	**<1.84**	**1.85-3.03**	**3.04-4.90**	**≥4.91**	***P*-trend**
All Cases					
No cases	239	266	280	247	0.11
$OR_{multivariable\text{-}adjusted}$[1] (95% CI)	1.0	1.25 (0.98,1.61)	1.37 (1.07,1.76)	1.21 (0.93,1.57)	
Gleason < 7*					
No. cases	191	209	205	171	0.49
$OR_{multivariable\text{-}adjusted}$[1] (95% CI)	1.00	1.26 (0.96, 1.64)	1.29 (0.99, 1.69)	1.09 (0.82, 1.45)	
Gleason 7-10*					
No. cases	35	49	63	65	0.004
$OR_{multivariable\text{-}adjusted}$[1] (95% CI)	1.00	1.51 (0.95, 2.42)	1.95 (1.24, 3.07)	1.88 (1.19, 2.97)	
	Continuous model [2]				
		OR	95%CI	p-value	
Gleason < 7		1.06	0.91, 1.23	0.44	
Gleason 7-10		1.39	1.09,1.76	0.01	
	Quartile of serum C-peptide concentration (ng/ml)				
Finasteride Arm	<1.84	1.85-3.03	3.04-4.90	≥ 4.91	*P*-trend
All Cases					
No. cases	193	165	203	194	0.55
$OR_{multivariable\text{-}adjusted}$[1] (95% CI)	1.0	0.72 (0.53,0.98)	0.84 (0.63,1.14)	0.86 (0.63,1.17)	
Gleason < 7*					
No cases	126	89	126	107	0.39

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	Quartile of serum C-peptide concentration (ng/ml)				
Placebo Arm	**<1.84**	**1.85-3.03**	**3.04-4.90**	**≥4.91**	***P*-trend**
$OR_{multivariable-adjusted}$[1] (95% CI)	1.00	0.61 (0.43, 0.87)	0.84 (0.60, 1.17)	0.77 (0.54, 1.09)	
Gleason 7-10*					
No. cases	60	63	70	81	0.67
$OR_{multivariable-adjusted}$[1] (95% CI)	1.00	0.87 (0.57, 1.32)	0.90 (0.59, 1.36)	1.07 (0.71, 1.62)	
	Continuous model[2]				
		OR	95%CI	p-value	
Gleason < 7		0.87	0.72, 1.05	0.16	
Gleason 7-10		0.96	0.76,1.20	0.69	

[1]Odds ratios are adjusted for age, race (white/non-white), family history of prostate cancer, insulin use at baseline, body mass index [wt(kg)/ht(m)^2], smoking (pack-years).

*The odds ratios for prostate cancer risk using both low-grade and high-grade disease (Gleason < 7 and Gleason 7-10) as outcomes in the same model were calculated using polytomous logistic regression with generalized logit link.; model includes both low-grade (Gleason < 7) and high-grade (Gleason 7-10), contrasted with no cancer.

[2]For the continuous models, the odds ratios represent the change in risk for each unit increase in [log (C-peptide)].

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Table 4

Adiposity-C-Peptide Interactions in Relation to High-Grade* Prostate Cancer in the PCPT (placebo arm only)

		C-Peptide < 3.08 ng/ml[1]			**C-Peptide ≥ 3.08 ng/ml[1]**		
Adiposity Measures	Total n	Cases (n)	OR[2]	95% CI	Cases (n)	OR[2]	95% CI
BMI							
Normal (BMI < 25 × C-peptide)	49	25	1.0 (ref)		24	1.43	0.77,2.66
Overweight (BMI 25.0-29.9 × C-peptide)	106	41	0.80	0.47,1.36	65	1.40	0.66, 2.96
Obese (BMI ≥ 30.0 × C-peptide)	57	19	1.62	0.84, 3.15	38	0.72	0.30, 1.72
Waist Circumference							
Waist < 102 cm × C-peptide	92	45	1.0 (ref)		47	1.50	0.95, 2.38
Waist ≥ 102 cm × C-peptide	104	34	0.98	0.58, 1.66	70	1.03	0.54, 1.97
Waist:Hip Ratio							
Waist:Hip < 1.0 × C-peptide	160	69	1.0 (ref)		91	1.56	1.09, 2.23
Waist:Hip ≥ 1.0 × C-peptide	36	10	0.73	0.35, 1.49	26	0.98	0.41, 2.33
Very High Risk [3]							
Low risk × C-peptide	145	63	1.0 (ref)		82	1.71	1.19, 2.47
Very high risk × C-peptide	46	15	1.20	0.57, 2.54	31	0.59	0.27, 1.28

[1]Median serum C-peptide concentration = 3.08 ng/ml.

[2]All odds ratios are adjusted for age (continuous), race (white vs nonwhite), family history of prostate cancer, insulin use at baseline, BMI continuous (except the model with BMI interactions), and pack-years of cigarettes smoked (continuous). P-values for all interaction tests are > 0.10.

[3]Very High-Risk is defined as: BMI >= 30 + waist circumference >= 102 cm, or BMI>=35 (see text for details).

*Polytomous regression used in analysis but only high-grade results are shown in Table 4.

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Table 5

Associations of Leptin with low and high-grade prostate cancer in the PCPT (n=3565)[1]

	Gleason <7 (n= 1224)			Gleason ≥ 7 (n= 486)		
	Odds Ratio [2]	**95% CI**	**p-trend**	**Odds Ratio [2]**	**95% CI**	**p-trend**
Model						
BMI* alone						
Normal (< 25.0)	1.0 (referent)		0.04	1.0 (referent)		0.03
Overweight (25.0-29.0)	0.83	0.70, 0.99		1.04	0.81, 1.33	
Obese (≥ 30.0)	0.80	0.64, 1.00		1.39	1.03, 1.87	
Leptin alone						
Q1 (<5.2 ng/ml)[3]	1.0 (referent)		0.003	1.0 (referent)		0.48
Q2 (5.2-8.6 ng/ml)	0.94	0.77, 1.16		1.22	0.92, 1.62	
Q3 (8.6-13.3 ng/ml)	0.88	0.71, 1.08		1.06	0.79, 1.43	
Q4 (> 13.3 ng/ml)	0.72	0.58, 0.90		1.18	0.88, 1.57	
BMI and Leptin						
Normal (< 25.0)	1.0 (referent)		0.62	1.0 (referent)		0.05
Overweight (25.0-29.0)	0.88	0.73, 1.07		1.03	0.78, 1.37	
Obese (≥ 30.0)	0.96	0.73, 1.26		1.46	1.01, 2.10	
Q1 Leptin[3]	1.0 (referent)		0.04	1.0 (referent)		0.65
Q2 Leptin	0.98	0.79, 1.21		1.18	0.87, 1.60	
Q3 Leptin	0.92	0.73, 1.16		0.98	0.70, 1.36	
Q4 Leptin	0.75	0.58, 0.98		0.98	0.68, 1.40	

[1] n= 3565 PCPT participants includes 1787 cases and 1778 controls; Gleason score not available on all men.

[2] Odds ratios are adjusted for age, race (white/non-white), family history of prostate cancer, treatment arm (finasteride or placebo), pack years of cigarette smoking and baseline insulin use.

[3] Quartiles of leptin are based on the distribution in the controls.

* $BMI = [wt(kg)/ht(m)^2]$