Obesity, Diabetes, and Risk of Prostate Cancer: Results from the Prostate Cancer Prevention Trial

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Abstract

Studies on the relationship between obesity and prostate cancer incidence are inconsistent. In part, this inconsistency may be due to a differential effect of obesity on low-grade and high-grade cancer or confounding of the association of obesity with prostate cancer risk by diabetes. We investigated the associations of obesity and diabetes with low-grade and high-grade prostate cancer risk. Data were from 10,258 participants (1,936 prostate cancers) in the Prostate Cancer Prevention Trial who all had cancer presence or absence determined by prostate biopsy. Multiple logistic regression was used to model the risk of total prostate cancer, and polytomous logistic regression was used to model the risk of low-grade and high-grade prostate cancer. Compared with men with body mass index < 25, obese men (body mass index ≥30) had an 18% [odds ratio (OR), 0.82; 95% confidence interval (95% CI), 0.69-0.98] decreased risk of low-grade prostate cancer (Gleason <7) and a 29% (OR, 1.29; 95% CI, 1.01-1.67) increased risk of high-grade prostate cancer (Gleason ≥7) or, alternatively, a 78% (OR, 1.78; 95% CI, 1.10-2.87) increased risk defining high-grade cancer as Gleason sum 8 to 10. Diabetes was associated with a 47% (OR, 0.53; 95% CI, 0.34-0.83) reduced risk of low-grade prostate cancer and a 28% (OR, 0.72; 95% CI, 0.55-0.94) reduced risk of high-grade prostate cancer. Associations of obesity or diabetes with cancer risk were not substantially changed by mutually statistical controlling for each other. Obesity increases the risk of high-grade but decreases the risk of low-grade prostate cancer, and this relationship is independent of the lower risk for prostate cancer among men with diabetes. (Cancer Epidemiol Biomarkers Prev 2006;15(10):1977–83)

Introduction

Many studies have examined the role of obesity in prostate cancer etiology, but their results have been conflicting and inconclusive (1, 2). Most studies have found no association between obesity and prostate cancer incidence (1, 3, 4), although some have reported associations of obesity with a lower risk of total cancer (5) or a higher risk of high-grade or nonlocalized cancer (6-8). In contrast to studies of cancer incidence, there is conclusive evidence that obesity is associated with a modest increased risk of prostate cancer mortality (9, 10). One potential explanation for these conflicting results is that obesity may differentially affect the development of aggressive and nonaggressive prostate cancers (11). Another potential explanation is that diabetes, which is associated with both obesity and decreased prostate cancer risk, could confound or distort observed associations of obesity with prostate cancer risk (12). Disentangling the associations among tumor grade, obesity, and diabetes could yield new insights into the role of obesity in the etiology and prevention of prostate cancer.

This study investigates the associations of obesity, including body mass index (BMI) and abdominal obesity, and diabetes with prostate cancer risk, using data from the Prostate Cancer Prevention Trial (PCPT; ref. 13). We hypothesize that (*a*) associations of obesity differ between low-grade and high-grade disease, and that (*b*) diabetes explains, at least in part, the observed associations of obesity with prostate cancer risk. Data from the PCPT include biopsy-determined presence or absence prostate cancer, uniform pathologic assessment of tumor grade, and standardized measures of weight and body circumferences collected by trained staff. This unique data set allows a comprehensive evaluation of our study hypotheses.

Materials and Methods

Study Design and Study Population. All data for this study were collected as part of the PCPT, 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 (13). Briefly, a total of 18,880 men ages ≥55 years with a normal digital rectal exam and prostate-specific antigen (PSA) level of ≤3 ng/mL, as well as no history of prostate cancer, severe benign prostate hyperplasia, or clinically significant coexisting conditions, were randomized to receive finasteride (5 mg/d) or placebo. During the PCPT, men underwent digital rectal exam and PSA measures annually, and a prostate biopsy was recommended for participants with an abnormal digital rectal exam or a PSA of ≥4.0 ng/mL. At the final study visit, all men not previously diagnosed with prostate cancer were offered an end-of-study biopsy. All biopsies were collected under transrectal ultrasonographic guidance and involved a minimum of six specimens (cores). All biopsies were reviewed to confirm the diagnosis of

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adenocarcinoma by both the pathologist at the local study site and at a central pathology laboratory. Discordant pathology interpretations were arbitrated by a referee pathologist, and concordance was achieved in all cases. Clinical stage was assigned locally. Tumors were graded centrally using the Gleason scoring system. Low-grade prostate cancer was defined as tumors with Gleason sum < 7, whereas high-grade prostate cancer was defined as tumors with Gleason sum ≥ 7. We also examined high-grade cancer defined as Gleason sum 8 to 10 due to the intermediate nature of Gleason sum 7 disease.

Of the 18,880 participants, we first excluded 7,539 (39.9%) men who did not have an end-of-study biopsy, which included 1,393 who died, 6,141 who were medically unable or refused, and 5 who had prostatectomy for reasons other than cancer, leaving 2,400 cases and 8,941 controls. We then excluded 173 cases diagnosed after the trial end date (June 23, 2003) and 90 cases diagnosed ≥180 days after their planned end-of-study visit, leaving 2,137 cases. We excluded cases diagnosed after the trial end date because we could not know whether or not they used finasteride after participants were unblinded to their treatment assignment. We excluded 99 controls whose end-of-study biopsies were completed ≥180 days before their planned end-of-study visit, leaving 8,842 controls. We included all controls with a negative biopsy completed at any time after their planned end-of-study visit because we assumed that these men would have been negative for cancer at the time of their scheduled visit. From a total 10,979 men, we further excluded 721 men who did not have anthropometric measurements, leaving 10,258 men for these analyses.

Data Collection. Extensive data are available on the demographic, medical, and lifestyle characteristics of PCPT participants. Details regarding age, race, education, family history of prostate cancer in first-degree relatives, and history of smoking were collected at baseline using self-administered questionnaires. For this analysis, race groups were categorized as African American, White, and ''other'', which included primarily Hispanic, Asian, or Pacific Island ancestry. Education status was classified as high school degree or less, some college or college degree, and advanced degree. Cigarette smoking at baseline was classified as current, former, or never. Diagnosis of and treatment for diabetes mellitus was assessed by self-report at the baseline clinic visit, each annual and 6-month clinic visit, and at every 3- and 9-month phone contact between scheduled clinic visits.

Anthropometric measures were collected by trained clinic staff following techniques recommended by Lohman et al. (14). Height and weight were assessed at the baseline clinic visit, and weight was assessed annually thereafter. Circumferences of the abdomen, waist, hip, and thigh were measured at 1-year after randomization. BMI was calculated as the 1-year post-randomization weight (kg) divided by height (m^2). We used BMI as a measure of overall obesity, and waist circumference, waist/hip ratio, and waist/thigh ratio as measures of abdominal (central) obesity.

Statistical Analysis. We contrasted means and distributions of demographic, health-related, and anthropometric variables of cases and controls and tested for statistically significant differences using *t* tests and χ^2 tests. We calculated odds ratios (OR) and 95% confidence intervals (95% CI) for risk of cancer using multiple logistic regression analysis. When cases were divided into low-grade and high-grade prostate cancer, we used polytomous logistic regression to calculate ORs for each case group versus controls (15). In these analyses, height, weight, waist circumference, and waist/thigh ratio were categorized by quartiles. BMI was categorized as <25, 25 to 26.9, 27 to 29.9, and ≥30, which approximated quartiles and was consistent with standard clinical definitions of obesity. Waist/hip ratio was categorized into four categories (<0.90, 0.90-0.93, 0.94-0.99, and ≥1.00) to capture variation in the tails of the distribution that would otherwise be obscured in analyses based on quartiles. Analyses were adjusted for age (<60, 60-64, 65-69, ≥70), race (White, African America, other), treatment (finasteride and placebo), and family history of prostate cancer in first-degree relatives (yes/no). Controlling for education and cigarette smoking did not affect variable estimates and were therefore not included in final models. We also examined the associations stratified by age (<65 and ≥65 years) and family history of prostate cancer (yes and no) and tested for potential effect modifications by including interaction terms in the model. Tests for linear trend across categories were done by using an ordinal variable corresponding to rank from lowest to highest category, as described by Breslow and Day (16).

We considered whether the effects of obesity on prostate cancer risk differed between the two PCPT arms because finasteride treatment did have significant effects on prostate cancer risk. We completed all analyses stratified by treatment arm and evaluated whether the associations in each arm were similar in both magnitude and direction. We also tested for significant multiplicative interactions by adding interaction terms in these models using the likelihood ratio test.

Results

Table 1 gives means and distributions of demographic, anthropometric, and health-related variables of cases and controls. Among the total 10,258 men in this analysis, 1,936 (18.9%) were diagnosed with prostate cancer; of these, 95.3% prostate cancers were local stage (T_1 + T_2), and 26.9% were high grade. Compared with controls, cases were older, more likely to be African Americans and have a family history of prostate cancer, and less likely to have been diagnosed with diabetes.

Table 2 gives associations of diabetes with prostate cancer risk. Men with diabetes had a 34% lower risk of prostate cancer compared with men without diabetes ($P < 0.05$), and this association was modestly stronger for low-grade compared with high-grade cancer. Further adjustment for BMI did not substantially alter these associations. The adjusted ORs for diabetes were 0.53 (95% CI, 0.34-0.83) for low-grade cancer and 0.72 (95% CI, 0.55-0.94) for high-grade cancer. These results did not differ between the finasteride and placebo study arms ($P_{interaction} = 0.54$).

Table 3 gives associations between anthropometric measures and prostate cancer risk. Height was positively associated with an increased risk of prostate cancer, and these associations were similar for both low-grade and high-grade disease. Compared with men in the lowest quartiles of height, those in the highest quartiles had a 22% increased risk of prostate cancer ($P_{trend} = 0.03$). All measures of obesity were inversely associated with risk of low-grade cancer, and these associations reached statistical significance for both BMI and waist circumference. Compared with men in the lowest quartiles of BMI and waist circumference, those in the highest quartiles had, respectively, an 18% and 22% reduced risk of low-grade cancer (both $P_{trend} < 0.05$). All measures of obesity were positively associated with risk of high-grade cancer, and associations reached statistical significance for BMI and weight. Compared with men in the lowest quartiles of BMI and weight, those in the highest quartiles had, respectively, a 29% and 44% increased risk of high-grade cancer (both $P_{trend} < 0.05$). Associations between these anthropometric measures and cancer risk were similar between two study arms, and all interaction tests were not significant (all $P > 0.33$). Results (ORs and 95% CIs) when high-grade cancer was restricted to Gleason sum 8 to 10 were 1.05 (0.62-1.76), 1.27 (0.78-2.06), and 1.78 (1.10-2.87) comparing men with

BMI < 25 with those with BMI 25 to 26.9, 27 to 29.9, and ≥30, respectively (P_{trend} = 0.01). We also examined these associations excluding cases with stage T_{1a} and T_{1b}, and results did not differ (data not shown).

Table 4 gives associations between BMI and prostate cancer risk stratified by age and family history. The associations of BMI with cancer risk were larger in men ages ≥65 compared with younger men, although interaction tests were not significant ($P_{interaction}$ = 0.19 and 0.80 for low-grade and high-grade cancer, respectively). Compared with older men with BMI < 25, older men with BMI ≥ 30 had a 28% decreased risk for low-grade disease (P_{trend} = 0.03) and a 56% increased risk for high-grade disease (P_{trend} = 0.01). There were no differences in associations of BMI with cancer risk between men with and without a family history of prostate cancer ($P_{interaction}$ = 0.23 and 0.35 for low-grade and high-grade cancer, respectively). These results did not differ substantially with or without controlling for diabetes, nor did they differ between study arms (all $P_{interaction}$ > 0.37).

We completed several analyses to examine whether there were unique contributions of abdominal obesity to prostate cancer risk beyond those described previously in Tables 3 and 4 for BMI alone. These models examined whether each of the three measures of abdominal obesity, waist circumference, waist/hip ratio, and waist/thigh ratio were associated with cancer risk after controlling for BMI (as a continuous variable). After controlling for BMI, all associations of abdominal obesity with cancer risk given in Table 3 were attenuated, and the significant association of waist circumference, comparing the highest to lowest quartiles, with decreased risk of low-grade disease was attenuated to 0.80 (95% CI, 0.62-1.03). There were no significant associations of abdominal obesity with cancer risk in subgroups defined by age or treatment arm. There were, however, significant associations of abdominal obesity with cancer risk in models stratified by family history, which also differed by treatment arm (Table 5). Trends for all measures of abdominal obesity were similar but reached statistical significance and are therefore only reported for waist circumference. Among men with a family history of prostate cancer in the placebo arm, there was a >2-fold increased risk of prostate cancer, comparing the highest to lowest quartiles of waist circumference (P_{trend} = 0.02), and this association was similar for both low-grade and high-grade disease (45% and 31% increased risk per 10 cm, respectively). In the finasteride arm, there were no associations of abdominal obesity with cancer risk among men with a family history of prostate cancer. Among men with no family history of prostate cancer, waist circumference was not associated with risk except for low-grade cancer in the finasteride arm, among whom each additional 10 cm of waist circumference was associated with a 22% decreased risk.

We also examined further the positive association of height with cancer risk given in Table 3. The association of height with risk remained statistically significant after controlling for BMI. In stratified analyses, there were no associations of height with risk of total, low-grade or high-grade cancer among men with BMI < 25 or ≥ 30. Among men with BMI between 25 and 30, height was significantly associated with increased risk of low-grade cancer (highest versus lowest quartile: OR, 1.41; 95% CI, 1.08-1.83) and weakly but not significantly associated with high-grade cancer (OR, 1.19; 95% CI, 0.79-1.81).

Table 1. Demographic, anthropometric, and health-related characteristics of prostate cancer cases and controls, the PCPT

	Cases (n = 1,936)	Controls (n = 8,322)	P*
Age (y)			
$\bar{X}$ ± SD	63.7 ± 5.6	62.6 ± 5.4	<0.0001
<60 (n, %)	525 (27.1)	2,798 (33.6)	<0.0001
60-64	602 (31.1)	2,699 (32.4)	
65-69	487 (25.2)	1,826 (22.0)	
70+	322 (16.6)	999 (12.0)	
Race (n, %)			
White	1,803 (93.1)	7,767 (93.3)	0.0003
African American	86 (4.5)	253 (3.1)	
Other	47 (2.4)	302 (3.6)	
Family history of prostate cancer (n, %)			
Yes	410 (21.2)	1304 (15.7)	<0.0001
Smoking (n, %)			
Nonsmoker	692 (35.7)	2,859 (34.4)	0.52
Former smoker	1,117 (57.7)	4,897 (58.9)	
Current smoker	127 (6.6)	561 (6.8)	
Diabetes (n, %)			
Yes	92 (4.8)	589 (7.1)	0.0002
Finasteride (n, %)			
Yes	782 (40.4)	4,213 (50.6)	<0.0001
Height (in.)			
$\bar{X}$ ± SD	70.0 ± 2.9	69.9 ± 2.8	0.20
Weight (lbs.)			
$\bar{X}$ ± SD	191.9 ± 29.6	192.7 ± 30.7	0.34
Waist (cm)			
$\bar{X}$ ± SD	102.1 ± 10.1	102.3 ± 10.4	0.30
Hips (cm)			
$\bar{X}$ ± SD	104.3 ± 7.9	104.5 ± 8.1	0.28
Thigh (cm)			
$\bar{X}$ ± SD	56.4 ± 5.6	56.5 ± 5.6	0.35
BMI (kg/m^2)			
$\bar{X}$ ± SD	27.6 ± 4.1	27.7 ± 4.1	0.11
<25 (%)	27.1	25.1	0.34
25-27	22.4	23.2	
27-29	27.9	28.3	
≥30	22.6	23.4	
Waist/hip ratio			
$\bar{X}$ ± SD	0.98 ± 0.05	0.98 ± 0.05	0.78
Waist/thigh ratio			
$\bar{X}$ ± SD	1.82 ± 0.18	1.82 ± 0.19	0.89
Histologic grade (n, %)			
Low (Gleason sum: 2-6)	1,300 (67.1)		
High (Gleason sum: ≥7)	521 (26.9)		
Unknown	115 (5.9)		
Clinical stage (n, %)			
T_{1a}	272 (14.0)		
T_{1b}	126 (6.5)		
T_{1c}	991 (51.2)		
T_{2a}	275 (14.2)		
T_{2b}	108 (5.6)		
T_{2c}	73 (3.8)		
T_3	32 (1.6)		
T_4	0		
Unknown	59 (3.1)		

*P of χ^2 test for categorical variables or of t test for continuous variables.

Table 2. Associations of diabetes with risk of prostate cancer, the PCPT

	n (cases/controls)	Adjusted*	Adjusted including BMI†
Total cancers			
Diabetes			
No	1,844/7,733	1.00	1.00
Yes	92/589	0.66 (0.52-0.82)	0.66 (0.52-0.83)
Low-grade cancer			
Diabetes			
No	1,236/7,733	1.00	1.00
Yes	64/589	0.56 (0.36-0.87)	0.53 (0.34-0.83)
High-grade cancer			
Diabetes			
No	499/7,733	1.00	1.00
Yes	22/589	0.69 (0.53-0.90)	0.72 (0.55-0.94)

*Adjusted for age, race, treatment, and family history of prostate cancer in first-degree relatives.
†Adjusted for age, race, treatment, family history of prostate cancer in first-degree relatives, and BMI.

Table 3. Associations of anthropometric variables with risk of prostate cancer, the PCPT

Variables	Quartiles*				P_{trend}
	1	2	3	4	
Height (m)	<1.72	1.72-1.78	1.79-1.82	≥1.83	
Total prostate cancer	1.00	1.07 (0.94-1.23)	1.07 (0.93-1.23)	1.22 (1.05-1.43)	0.03
Low-grade cancer	1.00	1.05 (0.90-1.23)	1.05 (0.90-1.24)	1.25 (1.04-1.50)	0.04
High-grade cancer	1.00	1.17 (0.92-1.47)	1.11 (0.87-1.42)	1.18 (0.88-1.57)	0.28
Weight (kg)	<78.0	78.0-85.7	85.8-95.2	≥95.3	
Total prostate cancer	1.00	1.06 (0.93-1.22)	1.06 (0.92-1.22)	1.06 (0.92-1.23)	0.42
Low-grade cancer	1.00	0.95 (0.81-1.13)	1.01 (0.86-1.19)	0.91 (0.77-1.08)	0.45
High-grade cancer	1.00	1.37 (1.07-1.77)	1.16 (0.90-1.51)	1.44 (1.11-1.86)	0.03
BMI (kg/m^2) †	<25.0	25.0-26.9	27.0-29.9	≥30	
Total prostate cancer	1.00	0.91 (0.79-1.05)	0.96 (0.83-1.10)	0.96 (0.83-1.10)	0.67
Low-grade cancer	1.00	0.88 (0.74-1.04)	0.88 (0.75-1.04)	0.82 (0.69-0.98)	0.03
High-grade cancer	1.00	0.97 (0.75-1.27)	1.09 (0.85-1.40)	1.29 (1.01-1.67)	0.04
Waist (cm)	<95	95-100	101-107	≥108	
Total prostate cancer	1.00	0.98 (0.85-1.13)	1.02 (0.89-1.18)	0.93 (0.81-1.18)	0.50
Low-grade cancer	1.00	0.94 (0.79-1.11)	1.00 (0.85-1.18)	0.78 (0.66-0.93)	0.02
High-grade cancer	1.00	1.05 (0.81-1.37)	1.01 (0.77-1.31)	1.27 (0.98-1.63)	0.09
Waist/hip ratio ‡	<0.90	0.90-0.93	0.94-0.99	≥1.00	
Total prostate cancer	1.00	0.96 (0.76-1.21)	1.01 (0.82-1.24)	0.98 (0.80-1.22)	0.94
Low-grade cancer	1.00	0.95 (0.73-1.23)	0.92 (0.72-1.16)	0.87 (0.68-1.11)	0.21
High-grade cancer	1.00	0.93 (0.61-1.42)	1.04 (0.71-1.52)	1.11 (0.76-1.64)	0.25
Waist/thigh ratio	<1.70	1.70-1.79	1.80-1.91	≥1.92	
Total prostate cancer	1.00	1.03 (0.89-1.19)	0.96 (0.83-1.11)	0.97 (0.84-1.13)	0.52
Low-grade cancer	1.00	0.99 (0.84-1.17)	0.90 (0.75-1.07)	0.93 (0.78-1.10)	0.26
High-grade cancer	1.00	1.17 (0.90-1.51)	1.07 (0.82-1.39)	1.08 (0.83-1.41)	0.75

Note: Associations are adjusted for age, race, treatment, diabetes, and family history of prostate cancer in first-degree relatives.
*A total of 1,936 cases (1,300 low-grade cancer cases, 521 high-grade cancer cases, and 115 with unknown Gleason score) and 8,322 controls.
†Quartiles of BMI were also consistent with standard clinical definitions of obesity.
‡Categories based on cut points selected after examination of variable distribution. *n* in each category: total (675, 1,634, 4,211, 3,478), low-grade cancer (640, 1,551, 3,939, 3,249) and high-grade cancer (579, 1,411, 3,610, 3,017).

Discussion

In this study of 10,258 men with biopsy-determined presence or absence of prostate cancer, we found that obesity, defined as BMI ≥ 30, was associated with an 18% decreased risk of low-grade cancer (Gleason <7) and a 29% increased risk of high-grade cancer (Gleason ≥7). In analysis restricting high-grade cancer to Gleason sum 8 to 10, obesity was associated with a considerably larger 78% increased risk. Diabetes was associated with a 47% reduced risk of low-grade cancer and a 28% reduced risk of high-grade cancer. There was no unique contribution of abdominal obesity to cancer risk beyond that for BMI, except in subgroups defined by family history of prostate cancer and study treatment arm. Among placebo arm men with a family history of prostate cancer, risk of total cancer (high and low grade combined) increased ~4% with each additional cm in waist circumference. In finasteride arm men with no family history of prostate cancer, risk of low-grade cancer decreased ~2% for each additional centimeter of waist circumference. Finally, height was positively associated with increased risk of low-grade cancer but only among men with BMI between 25 and 30.

The findings presented here support a hypothesis proposed recently by Freedland et al. that obesity differentially affects the development of aggressive and nonaggressive prostate cancer (11). If this hypothesis is true, then studies of obesity that do not stratify by cancer grade or other measure of disease aggressiveness may detect little or no association of obesity with this cancer's risk. Indeed, of the 23 studies that did not examine cancer separately by grade or stage (1, 4, 17-21), only four reported significant positive associations with risk (19, 22-24), and one reported significant inverse associations with risk (21). Three studies have examined a subgroup of ''aggressive'' cancers in addition to total cancer (3, 25, 26), defining aggressive cancers as high grade, advanced stage, or a combination of these two, and none found obesity significantly

Table 4. Associations between BMI and low-grade and high-grade prostate cancer, stratified by age and family history of prostate cancer, the PCPT

Variables	Grade	*n* (cases/controls)	BMI (kg/m^2), OR (95% CI)				P_{trend}
			<25.0	25.0-26.9	27.0-29.9	≥30	
Age*							
<65	Low	388/2,798	1.00	0.99 (0.80-1.23)	0.94 (0.77-1.16)	0.89 (0.72-1.11)	0.27
	High	112/2,798	1.00	0.88 (0.61-1.26)	0.92 (0.66-1.28)	1.03 (0.73-1.45)	0.82
≥65	Low	912/5,524	1.00	0.73 (0.56-0.94)	0.80 (0.62-1.03)	0.72 (0.55-0.96)	0.03
	High	409/5,524	1.00	1.03 (0.70-1.51)	1.23 (0.86-1.78)	1.56 (1.07-2.27)	0.01
Family history †							
No	Low	1,020/7,018	1.00	0.89 (0.74-1.07)	0.86 (0.72-1.03)	0.81 (0.67-0.98)	0.03
	High	418/7,018	1.00	0.95 (0.71-1.27)	1.08 (0.82-1.42)	1.29 (0.97-1.71)	0.07
Yes	Low	280/1,304	1.00	0.81 (0.56-1.18)	0.97 (0.68-1.38)	0.87 (0.60-1.26)	0.67
	High	103/1,304	1.00	1.06 (0.58-1.93)	1.14 (0.64-2.04)	1.35 (0.76-2.41)	0.28

*Adjusted for race, diabetes, treatment, and family history of prostate cancer in first-degree relatives.
†Adjusted for age, race, diabetes, and treatment.

Table 5. Associations between waist circumference and risk of low-grade and high-grade prostate cancer, stratified by treatment and family history of prostate cancer, the PCPT

Variables	*n* (cases/controls)	Waist circumference (cm), OR (95% CI)				P_{trend}	Continuous model (per 10 cm)
		<95	95-100	101-107	≥108		
Placebo arm							
Family history							
No	869/3,495	1.00	1.07 (0.86-1.32)	1.06 (0.84-1.33)	0.87 (0.64-1.18)	0.56	0.95 (0.84-1.08)
Yes	223/659	1.00	1.08 (0.68-1.71)	1.45 (0.88-2.40)	2.12 (1.10-4.11)	0.02	1.40 (1.05-1.87)
No family history							
Low grade	672/3,495	1.00	0.98 (0.77-1.25)	1.07 (0.83-1.39)	0.80 (0.56-1.14)	0.38	0.96 (0.83-1.11)
High grade	197/3,495	1.00	1.07 (0.69-1.66)	0.94 (0.59-1.52)	0.94 (0.52-1.72)	0.96	0.90 (0.71-1.14)
Have family history							
Low grade	175/659	1.00	0.98 (0.58-1.67)	1.62 (0.92-2.85)	2.54 (1.20-5.40)	0.01	1.45 (1.05-2.02)
High grade*	48/659	—	—	—	—	—	1.31 (0.76-2.32)
Finasteride arm							
Family history							
No	553/3,440	1.00	0.79 (0.61-1.03)	0.71 (0.54-0.94)	0.66 (0.46-0.94)	0.01	0.86 (0.74-1.00)
Yes	155/636	1.00	0.90 (0.53-1.52)	1.49 (0.87-2.57)	1.11 (0.55-2.22)	0.36	1.02 (0.76-1.36)
No family history							
Low grade	339/3,440	1.00	0.78 (0.57-1.07)	0.71 (0.50-1.01)	0.51 (0.32-0.82)	0.01	0.78 (0.64-0.94)
High grade	214/3,440	1.00	0.84 (0.56-1.27)	0.66 (0.42-1.05)	0.83 (0.48-1.45)	0.29	0.92 (0.73-1.16)
Have family history							
Low grade	102/636	1.00	0.76 (0.40-1.43)	1.28 (0.67-2.45)	0.77 (0.32-1.82)	0.95	0.96 (0.68-1.38)
High grade*	53/636	—	—	—	—	—	1.15 (0.72-1.86)

NOTE: Associations adjusted for age, race, diabetes, and BMI.
*Model could not be fit due to small numbers in certain cells.

associated with total or aggressive disease. Finally, seven studies have reported associations stratified by grade and/or stage (6-8, 27-30). Of the studies that stratified by grade, two found that obesity was significantly associated with increased risk of high-grade cancer and not associated with low-grade cancer (7, 8), and one found that obesity was associated with decreased risk for both low-grade and high-grade cancer (30). Of the studies that stratified by stage, two found an increased risk for regional/distant disease and no association with local disease (6, 27), and two found no associations with either local or regional/distant disease (28, 29). Thus, although the literature on obesity and cancer incidence is quite inconsistent, there is growing evidence that obesity may increase the risk of high-grade or regional/distant disease. Nevertheless, the differences in study populations, definitions of obesity, and classifications of aggressive disease make summary interpretation of this literature difficult.

Several mechanisms could explain the associations of obesity with prostate cancer risk, but one of the most likely is through steroid hormones. Obesity in men is associated with modestly lower levels of testosterone (31), substantially lower levels of sex hormone–binding globulin, and higher levels of estrogens (32). In contrast to the accepted dogma that high testosterone levels increase risk, more recent studies of steroid hormones and prostate cancer risk report that (*a*) testosterone is associated with reduced risk of high-grade and increased risk of low-grade disease (33-36), and (*b*) that estradiol is associated with decreased risk of ''nonaggressive'' cancer but not aggressive cancer (37). Thus, taken together, the net effect of obesity-related changes in sex hormone concentrations supports the biological plausibility of our findings.

The associations of abdominal obesity with risk were very complex and, because they differed by treatment arm, are difficult to interpret. These highly stratified analyses could have led to spurious findings; thus, we feel it parsimonious to report our results but interpret only those for the placebo arm, given the effects of finasteride treatment on cancer risk (13). In the placebo arm, abdominal obesity was associated with increased risk of both low-grade and high-grade cancer only among men with a family history of prostate cancer. Abdominal obesity may contribute uniquely to cancer risk because abdominal obesity is more strongly associated with increased insulin, insulin-like growth factors (IGF), and leptin than BMI alone, and all of these factors may influence prostate growth and carcinogenesis (38, 39). We know of no similar findings reported for prostate cancer, but the Iowa Women's Health Study reported an analogous finding for women with a family history of breast cancer, among whom those in highest quartile of waist/hip ratio had a 2-fold increased risk of progesterone receptor–negative breast cancer (40). Genetic factors associated with family history may confer a unique susceptibility to the metabolic abnormalities that are associated with abdominal obesity, which may be shared between women at high risk of breast cancer and men at high risk of prostate cancer. In our study, the association of abdominal obesity with prostate cancer was significant only for waist circumference, perhaps because waist circumference is a more specific measure of the metabolic and hormonal derangements related to abdominal adiposity than is waist/hip ratio (41, 42). It is plausible that the hormonal changes caused by finasteride treatment could modify effects of abdominal obesity on cancer risk, but this is speculative and cannot be readily addressed in this study. Clearly, these findings on abdominal obesity and prostate cancer risk require replication, and we hope future studies will collect the necessary data to do so.

Diabetes was strongly associated with a decreased risk of prostate cancer, which is consistent with most other studies that have examined this relationship (12). To our knowledge, however, this is the first study that examined the risk by low-grade and high-grade disease separately, for which we found a somewhat stronger association for low-grade disease. We also found that effects of diabetes were independent of BMI and abdominal obesity, which was unexpected because of the strong association of obesity with diabetes risk. This finding suggests that the reduced risk associated with diabetes is not simply due to confounding by obesity and further suggests that the mechanisms underlying the association of diabetes with prostate cancer risk may differ from those for obesity. Similar to obesity, diabetes is associated with lower testosterone levels (43), but unique mechanisms may involve the profoundly altered levels of insulin and bioactivity of IGF-1 in diabetics, both of which have been associated with risk of prostate cancer (44). The changes in insulin and IGF-1 in diabetics are related to time since diagnosis. Early in diabetes,

both insulin and IGF-1 are elevated, but insulin levels ultimately decrease to levels lower than nondiabetic men as a result of damage to pancreatic β cells (45). Furthermore, lowered insulin levels decrease IGF-1 bioactivity through modulating IGF-binding proteins (46). Although this suggests that associations of diabetes with cancer risk may differ by time since diabetes diagnosis, this hypothesis would be very difficult to test. Both prostate cancer and type 2 diabetes are chronic conditions, which rarely have an acute clinical onset. Both are underreported; their diagnosis is often serendipitous; and thus, their dates of diagnosis may not reflect the true onset of disease. Nevertheless, even when restricting our analyses to men with diabetes diagnosed after trial baseline and cancer diagnosed due to elevated PSA or abnormal digital rectal exam before the end of the trial, the associations of diabetes with cancer risk did not differ by the interval between first report of diabetes and cancer diagnosis. It is also possible that drugs used to treat diabetes or diabetes complications may decrease cancer risk. For example, metformin may reduce risk of cancer and cancer-related mortality in diabetics (47, 48), and statins used to treat hypercholesterolemia may also reduce prostate cancer risk (49). In future studies, we will have the opportunity to examine serum IGF and steroid hormone concentrations, as well as medication use, to better understand our findings of diabetes with reduced cancer risk.

We also found a positive association between height and risk of prostate cancer risk but only for low-grade disease among men with BMI between 25 and 30. Many studies have reported increased cancer risk associated with height (19, 26, 50), but none has reported the association stratified by grade. Several mechanisms could explain the association of height with prostate cancer risk. For example, adult height may reflect genetic or childhood environmental exposures that increase cancer risk (51, 52). Alternatively, our finding of an association for height among overweight men only suggests that residual confounding may also explain the association. Among men who are trim or obese, variation in height may not reflect a significant variation in hormonal or other factors related to risk, but among men in the relative narrow range of BMI between 25 and 30, height may be a more sensitive measure of these regulatory factors than BMI alone.

This study has several strengths. First, all men were screened for prostate cancer based on both PSA level and digital rectal exam during the trial and were determined by biopsy to have or not have cancer, which minimizes misclassification bias and eliminates detection bias attributable to PSA screening (53). Second, all tumors were uniformly evaluated for Gleason score, which minimizes the large intra-observer variability in assigning clinical grade. Third, all anthropometric measurements were collected by trained staff, improving the reliability of exposure assessments. This study also has several limitations. The small number of African American and other minority men limits our ability to examine whether these findings differ by race. Almost all cases were local stage; thus, we could not examine factors related to invasiveness and metastasis, but we could examine the effect of obesity on cancer grade independent of stage variation. Diabetes diagnosis was based on self-report and was likely underreported. Finally, the numbers of men in several subgroups (e.g., men with a family history of cancer who were diagnosed with high-grade disease) were relatively small, and there was inadequate statistical power to test for either main effects or interactions.

There are several important clinical implications from this study. First, obesity is associated with an increased risk of high-grade and thus clinically significant prostate cancer. Relatively few men diagnosed with low-grade prostate cancer die of the disease, but about 50% of the men diagnosed with high-grade disease die of prostate cancer within 10 years following diagnosis (54). Obesity increased the risk of Gleason sum 7 to 10 high-grade cancer by 29% and Gleason sum 8 to 10 cancer by 78%, which may be interpreted as moderate increases in risk. But the very high prevalence of obesity in the United States and the increasing rates of obesity around the world suggest that the population-attributable risk for prostate cancer due to obesity is substantial and will increase. In addition, for men with an already 2- to 4-fold increased risk due to a family history of prostate cancer, abdominal obesity may further increase risk by 2-fold. Reduced risk of prostate cancer should be added to the list of benefits of weight control, and this message may motivate men, especially men with a family history of prostate cancer, to better follow recommendations for healthful diets and increased physical activity.

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