Body Mass Index, Weight Change, and Risk of Prostate Cancer in the Cancer Prevention Study II Nutrition Cohort

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Abstract

Background: **Obesity has been associated with aggressive prostate cancer. The extent of this association, which varies by stage and grade, remains unclear. The role of recent weight change had not been previously examined.**
Methods: **We examined body mass index (BMI) and weight change in relation to incident prostate cancer by disease stage and grade at diagnosis among 69,991 men in the Cancer Prevention Study II Nutrition Cohort. Participants provided information on height and weight in 1982, and again at enrollment in 1992. During follow-up through June 30, 2003 (excluding the first 2 years of follow-up), we documented 5,252 incident prostate cancers. Cox proportional hazards models were used to estimate rate ratios (RR) and 95% confidence intervals (95% CI).**

Results: **The association between BMI in 1992 and risk of prostate cancer differed by stage and grade at diagnosis. BMI was inversely associated with risk of nonmetastatic low-grade prostate cancer (RR, 0.84; 95% CI, 0.66-1.06), but BMI was positively associated with risk of nonmetastatic high-grade prostate cancer (RR, 1.22; 95% CI, 0.96-1.55) and risk of metastatic or fatal prostate cancer (RR, 1.54; 95% CI, 1.06-2.23). Compared with weight maintenance, men who lost >11 pounds between 1982 and 1992 were at a decreased risk of nonmetastatic high-grade prostate cancer (RR, 0.58; 95% CI, 0.42-0.79).**
Conclusion: **Obesity increases the risk of more aggressive prostate cancer and may decrease either the occurrence or the likelihood of diagnosis of less-aggressive tumors. Men who lose weight may reduce their risk of prostate cancer.** (Cancer Epidemiol Biomarkers Prev 2007;16(1):63–9)

Introduction

Body mass index (BMI), a measure of body weight relative to height, is consistently used as an estimate of adiposity. BMI has been positively associated with incidence (1) and mortality (2) from a variety of adult cancers. Weight gain has been consistently associated with increased risk of postmenopausal breast cancer (3-5), and a recent study has shown that weight loss after menopause is associated with lower risk of breast cancer (5). There is little information, however, on the effect of weight change (gain or loss) on other cancer sites (6, 7).

Early prospective studies of adult BMI and the incidence of all prostate cancer have been markedly null (7-19), with only three European prospective studies reporting increasing risk of total incident prostate cancer with increasing BMI (20-22), and one American study finding that adult BMI was associated with decreased prostate cancer risk among men diagnosed before age 60 or those with a family history of prostate cancer (23). It is important to note, however, that all these studies examined incident prostate cancer cases regardless of stage or grade; given that prostate cancer has a highly variable natural history, which can range from rapid disease progression measured in months to a more indolent form in which survival can be measured in decades (24), it seems prudent to examine whether obesity may differentially affect aggressive versus nonaggressive disease. Indeed, despite the largely null

association between obesity and overall prostate cancer risk, adult BMI has been associated with the risk of more advanced prostate cancer and prostate cancer mortality in seven out of nine prospective studies (12, 13, 23, 25-29; ref. 25 includes results from two cohorts), and with higher recurrence rates after radical prostatectomy or radiotherapy treatment (30-33), suggesting that obesity may influence prostate cancer aggressiveness and progression.

The role of weight change on prostate cancer risk has been examined only in the Netherlands cohort (7). In that study, weight gain (from age 20 to age at study entry) was associated with slightly lower prostate cancer incidence, but the association did not persist after adjustment for BMI at age 20. Of note, weight at age 20 was recalled by middle-aged participants upon enrollment into the study. Thus, no study to date has used prospectively collected BMI data to assess whether weight change in later adult life could affect the risk of being diagnosed with prostate cancer.

We examined the association between adult BMI and prostate cancer incidence by stage and grade at diagnosis in a large cohort of adult U.S. men. In addition, we examined the association between weight change and prostate cancer incidence using weight prospectively reported at enrollment in 1992 and ~10 years before enrollment.

Materials and Methods

Study Population. Men in this study were selected from among the 86,404 male participants in the Cancer Prevention Study II (CPS-II) Nutrition Cohort (hereafter referred to as the Nutrition Cohort), a prospective study of cancer incidence and mortality among 184,190 U.S. men and women (34). The Nutrition Cohort is a subgroup of the ~1.2 million participants in the CPS-II, a prospective mortality study established

by the American Cancer Society in 1982 (35). Members of the CPS-II mortality cohort who resided in states with population-based cancer registries (21 states) and were 50 to 74 years of age in 1992 were invited to participate in the Nutrition Cohort by completing a mailed questionnaire. The recruitment and characteristics of Nutrition Cohort participants are described in detail elsewhere (34). All aspects of the CPS-II Nutrition Cohort study were approved by the Emory University Institutional Review Board.

At enrollment in 1992, participants completed a self-administered mailed questionnaire that included demographic, medical, anthropometric, behavioral, environmental, occupational, and dietary factors. Follow-up questionnaires were sent to cohort members in 1997, 1999, 2001, and 2003 to update exposure information and to ascertain newly diagnosed cancers. The response rate among living participants for each of the follow-up questionnaires (after multiple mailings) was at least 89%. For the present study, the follow-up period ended on June 30, 2003.

In this analysis, we excluded 3,208 men who were lost to follow-up (i.e., they were not known to be dead at the time of the first follow-up questionnaire in 1997 but did not return the 1997 follow-up questionnaire or any subsequent questionnaire). We also excluded men who reported any prevalent cancer (except nonmelanoma skin cancer) at baseline ($n = 9,022$), those whose self-report of prostate cancer on the 1997 questionnaire could not be verified or had conflicting information on the year of prostate cancer diagnosis ($n = 215$). We also excluded men with missing or extreme values (≤ 0.1 percentile or ≥ 99.9 percentile) of BMI in 1992 ($n = 1,186$). To limit the possible effect of weight loss due to any unrecognized disease, we excluded the first 2 years of follow-up ($n = 2,782$). After exclusions, the analytic cohort consisted of 69,991 men. Men whose self-report of prostate cancer in the 1999 or subsequent questionnaires could not be verified ($n = 620$) and men with stage A1 (T_{1A}) prostate cancer ($n = 109$) contributed person-time to the analysis up to the date of the last questionnaire on which they reported no history of prostate cancer or the date of their stage A1 prostate cancer diagnosis, and were not considered to be cases. Stage A1 prostate cancers were not included as cases because these lesions are detected incidentally at the time of the surgery for benign prostatic hyperplasia and tend to be relatively innocuous.

Identification of Cases of Prostate Cancer. We included a total of 5,252 incident primary prostate cancer cases diagnosed in the interval between enrollment in 1992 and June 30, 2003. Most incident cases of prostate cancer ($n = 5,147$) were initially identified through a self-report of prostate cancer on any of the questionnaires and subsequently verified by medical records ($n = 4,210$) or by linkage with state cancer registries ($n = 937$). A previous study linking cohort members to state cancer registries indicated that the ability of our respondents to report a past diagnosis of cancer was high (sensitivity, 0.93; specificity, 0.99; ref. 36). An additional 71 cases were ascertained as deaths due to prostate cancer through linkage with the National Death Index (37) among participants who did not report prostate cancer in any of the previous questionnaires. Additional clinical information was obtained for 34 of these 71 deaths through subsequent linkage with state cancer registries. Finally, 34 men who did not self-report prostate cancer on any of the questionnaires were identified as having prostate cancer during the process of verifying a different cancer through linkage with a state cancer registry.

We classified prostate cancer cases at diagnosis as follows: clinically nonmetastatic low-grade prostate cancer included cases with localized or regional invasive disease ($T_{1-3}N_0M_0$ or stage A, B, and C on the Jewitt-Whitmore staging system)

and Gleason score lower than 8 or WHO grade lower than 3 ($n = 4,138$); clinically nonmetastatic high-grade prostate cancer included cases considered to be localized or regionally invasive at diagnosis ($T_{1-3}N_0M_0$) but with Gleason score 8 or higher or grade 3 or higher ($n = 662$); metastatic or fatal cases included those diagnosed with stage D ($T_4N_xM_x$ or $T_xN_{1-2}M_x$ or $T_xN_xM_1$) prostate cancer or those for whom no information on stage at diagnosis was available and prostate cancer was listed as the primary cause of death on the death certificate ($n = 288$). High-grade prostate cancer tumor was defined as Gleason score 8 or higher due to the intermediate nature of Gleason sum 7 disease and the described Will Rogers phenomenon showing that contemporary Gleason score readings (2002-2004) from histology slides of diagnostic prostate tissue from 1990 to 1992 were statistically higher than the original readings (38). A total of 164 prostate cancer cases were excluded from this subanalysis due to missing information on Gleason score.

Anthropometric Assessment. On the baseline questionnaire in 1992, participants were asked to report their current weight. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Because all Nutrition Cohort participants were also participants in the larger CPS-II cohort, information on prospectively collected self-reported height and weight were also available from the 1982 CPS-II questionnaire.

BMI in 1992 was categorized into five categories: <25.0 (referent), 25.0 to <27.5, 27.5 to <30.0, 30.0 to <35.0, and ≥35.0 kg/m^2. These groupings were chosen based on statistical power and consistency with cut points that were proposed by the WHO (39) for underweight (<18.5), reference range (BMI, 18.5 to <25.0), overweight (BMI, 25.0 to <30.0), and obesity (BMI ≥30.0).

Adult weight change was calculated by subtracting weight reported in 1982 from weight reported in 1992. Weight change was categorized into mutually exclusive categories: weight gain of 6 to 10, 11 to 20, or ≥21 pounds, weight loss of 6 to 10, 11 to 20, or ≥21 pounds; men who reported little or no weight change (−5 to 5 pounds) comprised the referent category. These groupings were chosen arbitrarily in able to compare similar weight gain and weight loss and get stable estimates with each category.

Statistical Analysis. Cox proportional hazards modeling was used to examine the association between measures of obesity and incident prostate cancer while adjusting for each other and other confounding factors. All Cox models were stratified on the exact year of age at enrollment. Potential confounders included in the multivariate models were: race (White, Black, and other), education (less than high school, high school graduate, some college, college graduate, graduate school, missing), family history of prostate cancer in a brother and/or father (yes/no), smoking status (never/status at entry unknown, former, current), recreational physical activity as assessed by metabolic equivalents of energy expenditure units (METS; none, >0 to 7, >7 to 21, >21 to 28, >28 to 35, >35), and quintiles of total calorie intake. In addition, personal history of diabetes, which has been previously associated with lower risk of prostate cancer in this cohort (40), was included in all multivariate models as a time-dependent variable. History of recent prostate-specific antigen (PSA) testing (yes/no/ missing) was modeled as a time-dependent variable, updated with information from each follow-up questionnaire. Because history of PSA testing was first collected in the 1997 questionnaire, only follow-up after 1997 could be adjusted for history of PSA testing. BMI in 1982 and height in inches (<65, 65 to <67, 67 to <69, 69 to <71, 71 to <73, 73 to <75, ≥75) were included in multivariate models assessing the association between weight change and prostate cancer. Total intake of meat, fruit, calcium, and dairy were also examined as potential

confounders but were not included in the final models because such adjustments had negligible effects on the results (data not shown).

Trend tests for BMI were conducted by assigning the median BMI within each category to that category. We evaluated whether the associations between nonmetastatic low-grade prostate cancer, nonmetastatic high-grade and metastatic or fatal prostate cancer combined, and two measures of adiposity (BMI in 1992 and weight change) were modified by the confounders described above, and attained age. Effect modification was assessed using the likelihood ratio test to compare models with and without interaction terms.

Results

According to the 1992 WHO criteria, 35.9% (n = 25,102) of participants were of normal weight (BMI <25.0), 49.8% (n = 34,870) were overweight (BMI ≥25.0 to <30.0), and 14.3% (n = 10,019) were obese (BMI ≥30.0); mean BMI at baseline was 26.4 kg/m^2. A total of 43.8% (n = 30,457) of men reported little or no weight change between 1982 and 1992 (−5 to 5 pounds), 21.2% (n = 14,729) reported weight loss of >5 pounds, and 35.0% (n = 24,297) reported weight gain of ≥5 pounds.

The baseline characteristics of men in the cohort are presented according to BMI in Table 1. Men in the highest BMI categories were more likely to be Black, younger, and less educated, to be former smokers and exercise less, and were more likely to report diabetes and a diet high in

calories. Men in the lowest BMI category were more likely to report ever having been tested for PSA. Overall, 89% of men included in the analytic cohort reported ever being tested for PSA.

After multivariate adjustment, BMI in 1992 was not associated with risk of total prostate cancer (Table 2), even when the reference group was redefined as BMI <22.5 (data not shown). The association between BMI and prostate cancer incidence differed by stage and grade at diagnosis. The risk of nonmetastatic low-grade prostate cancer decreased significantly with increasing BMI (P_{trend} = 0.002). In contrast, the risk of nonmetastatic high-grade prostate cancer increased modestly with increasing BMI (P_{trend} = 0.03), although risk estimates were similar for men with a BMI of 27.5 to <30 [rate ratios (RR), 1.23; 95% confidence intervals (95% CI), 1.00-1.53], and for men with a BMI of ≥30 (RR, 1.22; 95% CI, 0.96-1.55). The risk of metastatic or fatal cancer increased steadily with increasing BMI (RR, 1.54; 95% CI, 1.06-2.23 for BMI≥30; P_{trend} = 0.05). There were too few men with a BMI≥35 who developed locally advanced disease, metastatic or fatal cancer to provide stable estimates, and therefore, these men were included in the ≥30 category. The association between nonmetastatic low-grade prostate cancer and BMI was stronger when having been diagnosed with diabetes was not included in the multivariate model (RR, 0.78; 95% CI, 0.61-0.98 for BMI ≥35 compared with BMI <25.0). Results for nonmetastatic high-grade and stage D or fatal prostate cancer did not differ substantially with or without controlling for diabetes. The associations between BMI in 1982 and risk of

Table 1. Age-adjusted percentages and medians of selected characteristics by categories of BMI (CPS-II Nutrition Cohort, 1992-2003)

	BMI in 1992 (kg/m^2)				
	<25.0	25.0 to <27.5	27.5 to <30.0	30.0 to <35.0	≥35.0
n	25,102	22,195	12,675	8,365	1,654
Race					
White	97.3	97.8	97.6	97.1	96.7
Black	0.9	1.1	1.4	1.8	2.4
Other	1.8	1.1	1.0	1.1	0.9
Age group					
<55	3.4	3.9	4.6	5.2	7.5
55-64	45.7	51.7	54.8	58.2	63.1
65-74	43.7	39.8	37.2	34.3	28.5
>75	7.2	4.7	3.4	2.3	1.0
Education level					
<High school	6.0	7.5	9.9	11.8	14.1
High school graduate	16.1	18.9	21.3	23.3	21.5
Some college	24.0	25.8	26.6	28.3	29.0
College graduate	23.7	22.5	19.8	16.9	15.8
Graduate school	29.7	24.8	21.5	18.8	19.0
Smoking status					
Never/unknown status	36.7	33.1	30.0	29.2	28.7
Former	52.6	58.4	62.4	63.1	65.1
Current	10.7	8.5	7.6	7.7	6.2
Family history of prostate cancer					
No	88.0	87.9	87.7	88.4	88.7
Yes	12.0	12.1	12.3	11.6	11.3
History of diabetes					
No	88.9	85.5	80.9	72.7	58.8
Yes	11.1	14.5	19.1	27.3	41.2
History of PSA testing*					
No	10.6	10.2	11.4	12.9	14.7
Yes	89.4	89.8	88.6	87.1	85.3
Height (in.)					
Median	70.0	70.0	71.0	70.0	70.0
Total calorie intake (kcal/d)					
Median	1,669	1,709	1,768	1,827	1,919
METs (h/wk)					
Median	13.5	10.5	7.5	4.5	3.5

NOTE: Percentages were adjusted to the age distribution of the entire study population and may not sum to 100 due to missing data.
*Ever reported PSA testing calculated from 1997 onward, excluding testing reported after prostate cancer diagnosis.

prostate cancer by grade and stage were similar to those for BMI in 1992 (data not shown).

Compared with weight maintenance (men with a change of ≤5 pounds in their weight), men who lost 11 to 20 pounds (RR, 0.84; 95% CI, 0.75-0.94) or >20 pounds (RR, 0.83; 95% CI, 0.69-1.01) between 1982 and 1992 were at a decreased risk of being diagnosed with prostate cancer. Weight loss of at least 11 pounds was strongly associated with decreased risk of being diagnosed with nonmetastatic high-grade prostate cancer (RR, 0.58; 95% CI, 0.42-0.79). Further adjustment for BMI in 1982 did not attenuate the strength of the association (Table 3). Both weight gain and weight loss seemed to predict for lower risk of nonmetastatic low-grade prostate cancer. No significant associations were seen between weight gain or weight loss and risk of metastatic or fatal prostate cancer.

The association between both measures of exposure (BMI in 1992 and weight change) and risk of all types of prostate cancer remained unchanged when analysis was restricted to White men (data not shown). We did not have power to assess these associations among Black men separately. We found no statistically significant interactions between BMI in 1992, or weight change and covariates included in the multivariate model. We observed no evidence of effect modification by attained age or family history of prostate cancer, as has been previously reported (23).

Discussion

Results from this large prospective study support the hypothesis that BMI differentially affects the development of nonaggressive and aggressive prostate cancer (41). The present findings of an increased risk of metastatic or fatal prostate cancer with increasing BMI are consistent in direction and magnitude with most previous studies (12, 13, 25-28). This is the first study, however, to suggest that recent weight loss may decrease the risk of being diagnosed with more aggressive prostate cancer.

Some metabolic changes associated with obesity are consistent with the hypothesis that obesity differentially affects the development of nonaggressive and aggressive prostate cancer (41). First, although testosterone contributes to the growth and progression of prostate cancer, it also plays an important role in maintaining the differentiation of normal prostatic epithelium and may play a similar role in tumor tissue (42). Serum testosterone levels decrease with increasing obesity (43, 44); thus, low testosterone levels may be associated with lower risk of nonaggressive prostate cancer and higher risk of less differentiated and more aggressive prostate cancer. Several studies have reported higher mean Gleason scores among patients with prostate cancer with lower serum testosterone levels (45, 46). Importantly, in the Prostate Cancer Prevention Trial, men treated with finasteride (an inhibitor of the conversion of testosterone to dihydrotestosterone, the primary androgen in the prostate) had lower overall prostate cancer incidence rates than the placebo group, but had higher rates of high-grade prostate cancer (47).

Other biological hypotheses that support the role of obesity in prostate cancer include alterations in insulin and bioavailable serum circulating insulin-like growth factor I (IGF-I) levels (48, 49). Circulating insulin levels increase linearly with increasing obesity, and insulin has been implicated in prostate cancer biology (50), with higher risk of prostate cancer (51), and with higher recurrence of the disease (52). Circulating concentrations of total IGF-I have been associated with higher risk of prostate cancer (53-56). However, the relationship between obesity and total circulating IGF-I levels does not seem to be linear. Several cross-sectional studies have shown the nonlinear relationship of IGF-I with adiposity and with the highest levels of total IGF-I at a BMI of ∼24 to 27 kg/m^2 (57, 58). Unfortunately, it is not known whether levels of total IGF-I in the circulation accurately reflect biological activity in prostate tissue.

Alternatively, although PSA screening did not modify the association between BMI or weight change and risk of prostate cancer, the prevalence of PSA screening was slightly lower among heavier men and the association between obesity and more aggressive prostate cancer may be due to differences in the detection or treatment of prostate cancer among obese men. PSA levels are lower among overweight and obese men

Table 2. RR and 95% CI values for the association between BMI and prostate cancer incidence (CPS-II Nutrition Cohort, 1992-2003)

	BMI in 1992 (kg/m^2)					P_{trend}
	<25.0	25.0 to <27.5	27.5 to <30.0	30.0 to <35.0	≥35.0	
All cases						
No. of cases	1,935	1,742	920	556	99	
Person-years	171,338	153,585	87,652	57,508	11,344	
RR (95% CI)*	1.00 (ref)	1.02 (0.95-1.08)	0.95 (0.88-1.03)	0.89 (0.81-0.98)	0.83 (0.68-1.02)	0.003
RR (95% CI)[†]	1.00 (ref)	1.02 (0.96-1.09)	0.98 (0.90-1.06)	0.94 (0.85-1.04)	0.91 (0.75-1.12)	0.14
Nonmetastatic low grade[‡]						
No. of cases	1,544	1,409	700	412	73	
Person-years	171,338	153,585	87,652	57,508	11,344	
RR (95% CI)*	1.00 (ref)	1.02 (0.95-1.09)	0.89 (0.81-0.97)	0.81 (0.72-0.90)	0.75 (0.59-0.94)	<0.0001
RR (95% CI)[†]	1.00 (ref)	1.03 (0.96-1.10)	0.92 (0.84-1.01)	0.86 (0.77-0.97)	0.84 (0.66-1.06)	0.002
Nonmetastatic high grade[‡]						
No. of cases	239	180	140	103		
Person-years	171,338	153,585	87,652	68,852		
RR (95% CI)*	1.00 (ref)	0.87 (0.71-1.05)	1.21 (0.98-1.49)	1.17 (0.93-1.48)[§]		0.06
RR (95% CI)[†]	1.00 (ref)	0.87 (0.72-1.06)	1.23 (1.00-1.53)	1.22 (0.96-1.55)[§]		0.03
Stage D or fatal cases						
No. of cases	92	104	46	46		
Person-years	171,338	153,585	87,652	68,852		
RR (95% CI)*	1.00 (ref)	1.40 (1.06-1.86)	1.14 (0.80-1.63)	1.57 (1.09-2.24)[§]		0.03
RR (95% CI)[†]	1.00 (ref)	1.41 (1.06-1.87)	1.14 (0.79-1.63)	1.54 (1.06-2.23)[§]		0.05

*Adjusted for age at interview.
[†]Adjusted for age at interview, race, education, family history of prostate cancer, total calorie intake, smoking status, history of PSA testing, history of diabetes, and physical activity.
[‡]One hundred and sixty-four nonmetastatic low-grade cases excluded due to missing Gleason score information.
[§]This value is for BMI 30 to <35 and BMI ≥35 groups combined.

Table 3. RR and 95% CI values for the association between recent weight change (1982-1992) and prostate cancer incidence (CPS-II Nutrition Cohort, 1992-2003)

| | Recent weight change from 1982-1992 (pounds) | | | | | | |
| | Weight loss | | | Loss or gain | Weight gain | | |
	−21+	−11 to −20	−6 to −10	−5 to 5	6-10	11-20	21+
All cases							
No. of cases*	113	349	541	2,450	751	687	322
Person-years	12,624	36,330	47,110	211,790	68,515	65,495	35,227
RR (95% CI) [†]	0.76 (0.63-0.92)	0.81 (0.72-0.90)	0.97 (0.89-1.07)	1.00 (ref)	0.97 (0.89-1.05)	0.95 (0.87-1.03)	0.85 (0.75-0.95)
RR (95% CI) [‡]	0.83 (0.69-1.01)	0.84 (0.75-0.94)	0.98 (0.89-1.08)	1.00 (ref)	0.98 (0.90-1.06)	0.96 (0.88-1.05)	0.88 (0.79-0.99)
RR (95% CI) [§]	0.84 (0.69-1.02)	0.84 (0.75-0.95)	0.98 (0.89-1.08)	1.00 (ref)	0.98 (0.90-1.06)	0.97 (0.89-1.05)	0.89 (0.79-1.00)
Nonmetastatic low grade [‖]							
No. of cases*	83	284	427	1,908	606	545	251
Person-years	12,624	36,330	47,110	211,790	68,515	65,495	35,227
RR (95% CI) [†]	0.73 (0.58-0.91)	0.86 (0.76-0.97)	1.00 (0.90-1.11)	1.00 (ref)	1.00 (0.91-1.09)	0.95 (0.86-1.05)	0.83 (0.73-0.95)
RR (95% CI) [‡]	0.81 (0.65-1.01)	0.90 (0.79-1.02)	1.01 (0.91-1.12)	1.00 (ref)	1.01 (0.92-1.10)	0.97 (0.88-1.07)	0.88 (0.77-1.00)
RR (95% CI) [§]	0.85 (0.68-1.06)	0.91 (0.81-1.04)	1.01 (0.91-1.13)	1.00 (ref)	1.01 (0.92-1.11)	0.98 (0.89-1.08)	0.89 (0.78-1.02)
Nonmetastatic high grade [‖]							
No. of cases*		45	66	332	87	129	
Person-years		48,954	47,110	211,790	68,515	100,722	
RR (95% CI) [†]		0.56 (0.41-0.77) [¶]	0.86 (0.66-1.12)	1.00 (ref)	0.84 (0.66-1.07)	0.88 (0.72-1.08) [**]	
RR (95% CI) [‡]		0.58 (0.42-0.79) [¶]	0.86 (0.66-1.12)	1.00 (ref)	0.85 (0.67-1.07)	0.90 (0.73-1.11) [**]	
RR (95% CI) [§]		0.55 (0.40-0.75) [¶]	0.85 (0.65-1.10)	1.00 (ref)	0.84 (0.67-1.07)	0.88 (0.71-1.08) [**]	
Stage D or fatal cases							
No. of cases*		31	28	137	33	57	
Person-years		48,954	47,110	211,790	68,515	100,722	
RR (95% CI) [†]		0.85 (0.58-1.26) [¶]	0.82 (0.55-1.24)	1.00 (ref)	0.81 (0.55-1.18)	1.02 (0.75-1.39) [**]	
RR (95% CI) [‡]		0.87 (0.59-1.30) [¶]	0.84 (0.56-1.26)	1.00 (ref)	0.80 (0.55-1.17)	0.99 (0.72-1.35) [**]	
RR (95% CI) [§]		0.83 (0.56-1.24) [¶]	0.83 (0.55-1.24)	1.00 (ref)	0.80 (0.54-1.17)	0.97 (0.71-1.33) [**]	

*Case numbers may not sum to total 5,252 due to exclusions of extreme values of weight in 1982 and missing data.
[†]Adjusted for age at interview.
[‡]Adjusted for age at interview, race, education, family history of prostate cancer, total calorie intake, smoking status, history of PSA testing, history of diabetes, height, and physical activity.
[§]Adjusted for age at interview, race, education, family history of prostate cancer, total calorie intake, smoking status, history of PSA testing, history of diabetes, height, physical activity, and BMI in 1982.
[‖]One hundred and sixty-four nonmetastatic low-grade cases excluded due to missing Gleason score information.
[¶]This value is for the weight loss of −11 to −20 and −21+ groups combined.
[**]This value is for the weight gain of 11 to 20 and 21+ groups combined.

compared with thin men despite larger prostate sizes (59, 60). Therefore, even with the same levels of PSA screening, a smaller proportion of obese men will have an abnormally high PSA result and undergo biopsy. Moreover, at the time of biopsy, the larger prostate makes the detection of an existent cancer more difficult.

In our study, the risk of being diagnosed with prostate cancer was decreased among men who experienced weight loss in the 10 years preceding enrollment, although the association was only statistically significant for men diagnosed with nonmetastatic high-grade prostate cancer, supporting a role for caloric restriction on prostate cancer carcinogenesis. Caloric restriction decreases cellular proliferation (61), enhances apoptosis (62), and delays prostate cancer development in genetically susceptible mice (63, 64). In addition, caloric restriction reduces tumor growth, lowers circulating levels of IGF-I, and decreases the expression of vascular endothelial growth factor in a human prostate cancer–transplanted mice model (65). Human data on caloric restriction are limited, however, and a recent randomized clinical trial to examine the effects of 6 months of caloric restriction among healthy men and women showed decreased levels of fasting insulin levels in the intervention group study (66). In addition, moderate weight loss following a weight loss diet has been associated with decreased levels of plasma insulin in several studies (67, 68).

The strengths of this study are its large size and prospectively collected information on weight at two different points in time, allowing us to examine the relationship between BMI and weight change separately for aggressive and nonaggressive prostate cancer. The association between BMI and prostate cancer, however, should be interpreted within the limitations

of the study. First, although BMI is an adequate measure of adiposity in young adults and middle-aged populations (69), it may be insufficient in older adults, such as the men included in this cohort. As people age, individuals may lose substantial amounts of lean body mass whereas maintaining the same weight, thus, reducing the validity of BMI as a measure of adiposity. Second, we used self-reported weight and height at study entry, both of which are subject to error (70). In addition, no data were collected on weight during childhood, which has been previously associated with decreased risk of prostate cancer (15).

In conclusion, the results of this study suggest that the association between obesity differs by prostate cancer stage and grade. Increased adiposity is associated with higher risk of more aggressive and more advanced prostate cancer, but may lower the risk of being diagnosed with less-aggressive tumors. An important finding from this study is that men who lose weight may reduce their risk of more aggressive prostate cancer, supporting a role of energy restriction on prostate cancer carcinogenesis.

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