Body Mass Index and Risk of Prostate Cancer in U.S. Health Professionals

Edward Giovannucci, Eric B. Rimm, Yan Liu, Michael Leitzmann, Kana Wu, Meir J. Stampfer, Walter C. Willett

The relationship between body mass index (BMI) and prostate cancer risk may be complex because obesity is associated with various hormonal factors and because the influence of BMI may differ according to whether the cancers are hereditary or sporadic. We used data from the Health Professionals Follow-Up Study, in which 2896 incident cases of prostate cancer were reported from February 1, 1986, through January 31, 2000, to determine prospectively whether BMI was associated with the risk of hereditary (men <60 years of age or with a positive family history of prostate cancer) and sporadic (men $\geqslant$60 years of age and without such a family history) prostate cancer. The risk of prostate cancer in men with a higher BMI ($\geqslant$30 kg/m^2) was lower than that in men with a lower BMI (23–24.9 kg/m^2) but only if they were younger (<60 years old) (relative risk = 0.52, 95% confidence interval = 0.33 to 0.83; P_{trend}<.001) or had a family history of prostate cancer (relative risk = 0.74, 95% confidence interval = 0.45 to 1.19; P_{trend} = .01). However, for groups with more sporadic cancers, BMI had a weak, non–statistically sig-

Affiliations of authors: E. Giovannucci, E. B. Rimm, M. J. Stampfer, W. C. Willett, Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, and Departments of Nutrition and Epidemiology, Harvard School of Public Health, Boston, MA; Y. Liu, K. Wu, Department of Nutrition, Harvard School of Public Health; M. Leitzmann, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD.

Correspondence to: Edward Giovannucci, MD, ScD, Harvard School of Public Health, 665 Huntington Ave., Boston, MA 02115 (e-mail: edward. giovannucci@channing.harvard.edu).

See "Notes" following "References."

nificant positive association with prostate cancer. We observed statistically significant interactions between BMI and age ($P_{interaction}<.001$, two-sided Wald test) and between BMI and family history of prostate cancer ($P_{interaction} = .006$, two-sided Wald test). Patterns for BMI and waist circumference were similar. Because obesity is associated with lower circulating concentrations of testosterone, our results suggest the hypothesis that androgens may play a more direct role for early-onset or hereditary prostate cancers than for sporadic prostate cancers. [J Natl Cancer Inst 2003;95:1240–4]

The results of numerous studies that have examined whether body mass was associated with the risk of prostate cancer have not been consistent, and most have not supported an association (1). The inconsistent results may be caused by the complex relationship between obesity and several hormones. For example, obesity in males is associated with lower circulating testosterone concentrations and higher estrogen concentrations (2–6), which could decrease the risk of prostate cancer, but obesity is also associated with higher insulin and free insulin-like growth factor-I (7–12) and lower sex hormone–binding globulin concentrations, which could possibly increase the risk (13–15). Heterogeneity in prostate cancer etiology by age and genetic factors may further complicate its relation with body mass index (BMI). A large proportion of prostate cancers that occur in relatively young men (e.g., <60 years old) or that are associated with a family history of prostate cancer probably have a strong genetic component (16). Sporadic cases of prostate cancer, in contrast, typically occur in older men without a family history of prostate cancer. Potential etiologic differences between hereditary and sporadic cases of prostate cancer have not been well studied.

In the Health Professionals Follow-Up Study, we previously reported results on BMI and prostate cancer risk that were based on data from 1369 incident cases of prostate cancer from February 1, 1986, through January 31, 1994. No appreciable association was observed with current BMI, although obesity around the time of puberty was associated with lower risk of aggressive

prostate cancer in adulthood (17). In the current study, we analyzed data that were based on 2896 cases of prostate cancer from February 1, 1986, through January 31, 2000, with a focus on more extreme ranges of BMI and on potential differences between sporadic (men ⩾60 years and without a positive family history of prostate cancer) and hereditary (men <60 years of age or with such a history) prostate cancers. This study was approved by the Institutional Review Board of the Harvard School of Public Health. Written informed consent to review medical information was obtained from all cancer patients.

Briefly, the Health Professionals Follow-Up Study is an ongoing prospective cohort study of 51 529 U.S. male health professionals, aged 40–75 years in 1986, who responded to a mailed questionnaire on lifestyle and medical history. Follow-up questionnaires were sent every 2 years thereafter to identify cancer diagnoses and to update exposure data. Deaths were reported by family members, the postal system, or the National Death Index. We estimate that we have ascertained more than 98% of the deaths and approximately 96% of the cases of prostate cancer in this cohort. More than 90% of the prostate cancers were confirmed with medical records.

On the 1986 baseline questionnaire, we asked the men to report their current height and weight and their weight at age 21 years. Current weight was also assessed on each biennial questionnaire. In 1987, we mailed a supplementary questionnaire and a tape measure to these men to obtain waist and hip circumference measurements. We used BMI (expressed as kg/m^2) to estimate total adiposity and waist circumference to estimate total abdominal fat. These measures were shown to be highly valid (18). We categorized BMI *a priori* to encompass a wide range of values. We used validated, self-administered, semiquantitative food-frequency questionnaires to assess diet in 1986, 1990, 1994, and 1998 (19). In 1986 and every 2 years thereafter, we used a validated questionnaire to assess leisure-time physical activity (20). Detailed lifetime tobacco use was assessed at baseline, and current smoking status was updated every 2 years. We began assessing prostate-specific antigen (PSA) screening on the biennial questionnaires in 1994. In 1990, the men reported whether their father or any

brothers had had a diagnosis of prostate cancer.

For analyses, we excluded men who reported cancer (other than nonmelanoma skin cancer) at baseline and men who did not adequately complete the dietary questionnaire. Each of the remaining 47 757 participants was followed beginning on the month of return of the baseline questionnaire until the month of diagnosis of prostate cancer, month of death from other causes, or the end of the study period (January 31, 2000). The end points for analysis were total prostate cancer (excluding stage T1a tumors), organ-confined prostate cancer, and advanced prostate cancer, defined as cancer that extended regionally to the seminal vesicle, other adjacent organs, pelvic lymph nodes, or distal organs at the time of diagnosis or that was fatal by the end of follow-up.

From February 1, 1986, when the study began, to January 31, 2000, we documented 2896 incident cases of prostate cancer after we excluded 68 cases of stage T1a cancer (⩽5% of tissue transurethrally resected was noted as incidental cancer by histologic examination). After determining that the data met the assumptions for Cox proportional hazards modeling, we used this method to control for established or suggested risk factors for prostate cancer (21) (*see* Table 1). All statistical tests were two-sided. For all analyses, results for age-adjusted and multivariable analyses were similar, so only multivariable results are presented. Baseline BMI in 1986 did not have a linear association with total prostate cancer incidence ($P_{trend} = .11$). However, a slight "inverse U"–shaped relationship was suggested, with modestly reduced risks in the lowest (<21 kg/m^2; relative risk [RR] = 0.86, 95% confidence interval [CI] = 0.69 to 1.06) and highest (⩾30 kg/m^2; RR = 0.87, 95% CI = 0.74 to 1.01) categories compared with the intermediate BMI category (23–24.9 kg/m^2), although a quadratic term for BMI was not statistically significant ($P = .52$). No obvious association was apparent for the advanced (extraprostatic) cases of prostate cancer. For the organ-confined cases, the lowest risk was observed in the two highest BMI categories and the overall test for (inverse) trend was statistically significant ($P = .02$).

We next considered the relationship between BMI and prostate cancer risk

across strata of age groups or family history of prostate cancer (Table 1). The risk of prostate cancer in men with a higher BMI ($\geq$30 kg/m^2) was lower than that in men with a lower BMI (23–24.9 kg/m^2) but only if they were younger (<60 years old) (RR = 0.52, 95% CI = 0.33 to 0.83) or had a family history of prostate cancer (RR = 0.74, 95% CI = 0.45 to 1.19). A strong inverse association was observed for men younger than 60 years (P_{trend}<.001). No clear pattern was observed for men in the intermediate (60–70 years) or in the oldest ($\geq$70 years) age group. The test for interaction between age and BMI was statistically significant ($P_{interaction}$<.001). Among men with a family history of prostate cancer, an inverse association was observed between BMI and the risk of prostate cancer (P_{trend} = .01). Among those with no family history of prostate cancer, in contrast, no overall association was observed. The P value for the test for interaction between BMI and a family history of prostate cancer was .006. Among men in the hereditary cancer–enriched group (Table 2), a strong inverse association between BMI and the risk of prostate cancer was apparent (P_{trend}<.001). Among men in the sporadic cancer–enriched group, a modest positive association between BMI and the risk of prostate cancer was observed for a BMI of less than 25 kg/m^2, and no overall association was apparent for higher values of BMI. The P value for this test for interaction was less than .001.

The patterns of the relationship between prostate cancer risk among strata of family history of prostate cancer and age group were similar for advanced, organ-confined, and total prostate cancers (data not shown). In addition, when we examined prostate cancer risk in relation to BMI 2–4 years before the diagnosis of prostate cancer, rather than to BMI at baseline, the associations were similar (for age interaction, P = .007; for family history interaction, P = .05; for age + family history interaction, P<.001). Similar to BMI, waist circumference was inversely associated with prostate cancer risk only among younger men and among those with a family history of prostate cancer ($P_{interaction}$ = .08 for age; $P_{interaction}$ = .003 for family history). As we reported previously *(17)*, BMI at age 21 years was inversely associated with extraprostatic prostate cancer (P_{trend} = .003) but not with organ-confined prostate cancer (P_{trend} = .64), and risk did not vary appreciably by age or family history.

As observed in many other studies, adult BMI was not appreciably associated with prostate cancer incidence. However, when we examined this relationship by strata enriched for hereditary cancers or for sporadic cancers as determined by age at diagnosis or family history of prostate cancer, BMI and waist circumference were strongly and inversely associated with the risk of prostate cancer only in the hereditary prostate cancer–enriched group. The large number of cases of prostate cancer, the highly statistically significant interactions, the consistent patterns observed for young age of onset and family history of prostate cancer (as distinct surrogates for sporadic or hereditary cancers, respectively), and similar findings for BMI and waist circumference make it improbable that the findings were caused by chance. Detection bias was unlikely to account for these associations because most prostate cancers were detected by PSA screening, and the

Table 1. Multivariable relative risk (RR)* of prostate cancer and 95% confidence interval (CI) by level of body mass index (BMI) stratified by age and by family history of prostate cancer in health professionals (1986–2000)

Factors	BMI (kg/m^2)						P_{trend}
	<21	21–22.9	23–24.9	25–27.4	27.5–29.9	$\geq$30	
Age <60 y							
No. with prostate cancer	17	76	127	132	29	22	
RR (95% CI)	1.12 (0.67 to 1.86)	1.18 (0.89 to 1.57)	1.0 (referent)	0.91 (0.71 to 1.17)	0.49 (0.32 to 0.73)	0.52 (0.33 to 0.83)	<.001
Age 60–70 y							
No. with prostate cancer	37	190	377	416	187	108	
RR (95% CI)	0.87 (0.60 to 1.22)	1.03 (0.87 to 1.23)	1.0 (referent)	0.86 (0.75 to 0.99)	0.97 (0.81 to 1.16)	0.90 (0.72 to 1.11)	.42
Age >70 y							
No. with prostate cancer	40	152	358	404	144	80	
RR (95% CI)	0.77 (0.55 to 1.06)	0.82 (0.68 to 1.00)	1.0 (referent)	0.94 (0.82 to 1.09)	0.94 (0.77 to 1.14)	0.97 (0.76 to 1.24)	.26
						$P_{interaction}$<.001†	
Family history of prostate cancer‡							
No. with prostate cancer	13	56	104	96	31	21	
RR (95% CI)	1.44 (0.79 to 2.60)	1.00 (0.71 to 1.39)	1.0 (referent)	0.73 (0.55 to 0.97)	0.72 (0.48 to 1.09)	0.74 (0.45 to 1.19)	.01
No family history of prostate cancer							
No. with prostate cancer	76	346	728	814	317	182	
RR (95% CI)	0.79 (0.62 to 1.00)	0.95 (0.84 to 1.08)	1.0 (referent)	0.92 (0.83 to 1.02)	0.92 (0.81 to 1.05)	0.90 (0.76 to 1.06)	.73
						$P_{interaction}$ = .006§	

*The RR for each category was computed as the rate among men in that specific category divided by the rate among men with BMI of 23–24.9 kg/m^2, the largest group in what is considered the normal range of BMI. We used Cox porportional hazards modeling to control for age; time period; height; smoking history; history of diabetes mellitus; racial group; vigorous activity level; total energy intake; and intakes of beef, pork, or lamb as a main dish, processed meat, fish, tomato sauce, α-linolenic acid, and calcium simultaneously. We also used it to compute 95% CIs. In the regression models, age (1-year intervals) and time period (2-year intervals) were controlled as variables. Tests for trends were conducted across categories controlling for multiple covariates by modeling BMI as a continuous variable in the multivariable model that included the covariates. P values are based on two-sided tests.

†We tested for statistical (multiplicative) interactions in separate models by using the Wald test of the cross-product term for BMI (continuous) and increasing age strata (0,1,2). The cross-product terms were included in Cox proportional hazards models that also controlled for age, BMI, family history, and other factors mentioned above.

‡N for family history analysis, number of cases does not add up to 2896 because of missing information on family history.

§Test for interaction using the Wald test of the cross-product term for BMI (continuous) and family history (0,1).

Table 2. Multivariable relative risk (RR)* of prostate cancer and 95% confidence interval (CI) by level of body mass index (BMI) stratified simultaneously by age and family history of prostate cancer in health professionals (1986–2000)

Factors	BMI (kg/m^2)						P_{trend}
	<21	21–22.9	23–24.9	25–27.4	27.5–29.9	≥30	
<60 y or a family history of prostate cancer†							
No. with prostate cancer	25	120	212	209	58	40	
RR (95% CI)	1.11 (0.73 to 1.68)	1.10 (0.88 to 1.38)	1.0 (referent)	0.82 (0.67 to 0.99)	0.62 (0.46 to 0.83)	0.64 (0.45 to 0.90)	<.001
≥60 y and no family history of prostate cancer							
No. with prostate cancer	64	284	624	708	290	165	
RR (95% CI)	0.76 (0.59 to 0.99)	0.92 (0.80 to 1.05)	1.0 (referent)	0.92 (0.83 to 1.03)	0.98 (0.85 to 1.12)	0.96 (0.80 to 1.14)	.28

$P_{interaction}$<.001‡

*Multivariable RR adjusted for age; time period; height; smoking history; history of diabetes mellitus; racial group; vigorous activity level; total energy intake; and intakes of beef, pork, or lamb as a main dish, processed meat, fish, tomato sauce, α-linolenic acid, and calcium. All statistical tests were two-sided.

†Number of cases does not add up to 2896 because of missing information on family history.

‡This value is based on the Wald test of the cross-product term for BMI (continuous) and hereditary prostate cancer risk (age <60 y or family history of prostate cancer = 1) or sporadic prostate cancer risk (age ≥60 y and no family history of prostate cancer = 0) in the multivariable model.

proportion of men who had a PSA test did not vary appreciably across levels of BMI (from 81% in the lowest strata to 83% in the highest strata).

Our results suggest that substantial heterogeneity exists in the etiologic factors associated with hereditary and sporadic prostate cancers. Hereditary prostate cancer is diagnosed an average of 6–7 years earlier than sporadic prostate cancer, and perhaps two-thirds of all prostate cancers diagnosed in men younger than age 60 years may be hereditary *(16),* possibly accounted for by autosomal dominant genes *(16)* or X chromosome–linked and recessive genes *(22).* The vast majority of prostate cancers that occur in older men (e.g., age >70 years) and in men with no family history of prostate cancer are sporadic. Studies have not found substantial differences in clinical features between hereditary and sporadic prostate cancers *(22),* suggesting that despite possible etiologic differences, hereditary and sporadic prostate cancers tend to converge in regard to clinical features.

The mechanism for the apparent decreased risk of prostate cancer conferred by obesity in the hereditary cancer–enriched group is unknown but may be associated with several hormones. Obesity in males is associated with lower concentrations of circulating total testosterone and sex hormone–binding globulin and with higher concentrations of estrogen *(2–4,23–25).* The high levels of circulating leptin in obese men may reduce androgen levels *(26).* The lower concentration of testosterone associated with higher BMI may be responsible for the decreased risk of prostate cancer. Of

note, a shorter CAG repeat length in exon 1 of the androgen receptor (AR) gene, associated with greater *in vitro* transactivation activity of AR *(27),* appears to be associated with an increased risk of prostate cancers that occur in younger men but not with prostate cancers that tend to occur in older men *(28).*

The opposing findings with regard to obesity and prostate cancer by age group and family history status suggest the following hypothesis: Increased androgen stimulation (e.g., by lower BMI, fewer AR CAG repeats, and/or higher testosterone levels) increases the risk for hereditary prostate cancer more than the risk for sporadic prostate cancer, which tends to occur later in life and appears to be less directly associated with androgen stimulation. If one of the prostate cancer–associated mutations is inherited through the germline, heightened androgenic stimulation may be sufficient to increase the incidence of prostate cancer. In contrast, those without an inherited susceptibility may generally require a strong environmental risk factor, such as chronic inflammation.

The major implications of our results are in understanding the etiology of prostate cancer. From a clinical or public health perspective, even if obesity lowers the risk of prostate cancer, its effects on general health status are overwhelmingly deleterious. Nonetheless, if we can understand the mechanisms underlying the inverse association between BMI and early-onset or familial prostate cancer, there may be implications in regard to identifying susceptible groups that may benefit from enhanced screening frequency or interventions. For example, if androgenicity is found to underlie the associations we observed for BMI, antiandrogen interventions could be targeted at younger men with a positive family history but may possibly be inappropriate for older men without a positive family history. Thus, the replication of these studies in other populations and further work in understanding the underlying mechanisms is warranted.

REFERENCES

(1) Nomura AM. Body size and prostate cancer. Epidemiol Rev 2001;23:126–31.

(2) Amatrauda JM, Harman SM, Pourmotabbed G, Lockwood DH. Decreased plasma testosterone and fractional binding of testosterone in obese males. J Clin Endocrinol Metab 1978;47:268–71.

(3) Zumoff B. Hormonal abnormalities in obesity. Acta Med Scand Suppl 1988;723:153–60.

(4) Field AE, Colditz GA, Willett WC, Longcope C, McKinlay JB. The relation of smoking, age, relative weight, and dietary intake to serum adrenal steroids, sex hormones, and sex hormone-binding globulin in middle-aged men. J Clin Endocrinol Metab 1994;79:1310–6.

(5) Vermeulen A, Kaufman JM, Deslypere JP, Thomas G. Attenuated luteinizing hormone (LH) pulse amplitude but normal LH pulse frequency, and its relation to plasma androgens in hypogonadism of obese men. J Clin Endocrinol Metab 1993;76:1140–6.

(6) Lima N, Cavaliere H, Knobel M, Halpern A, Medeiros-Neto G. Decreased androgen levels in massively obese men may be associated with impaired function of the gonadostat. Int J Obes Relat Metab Disord 2000;24:1433–7.

(7) Cotterill AM, Holly JM, Wass JA. The regulation of insulin-like growth factor binding protein (IGFBP)-1 during prolonged fasting. Clin Endocrinol (Oxf) 1993;39:357–62.

(8) Busby WH, Snyder DK, Clemmons DR. Radioimmunoassay of a 26,000-dalton plasma insulin-like growth factor-binding protein: control by nutritional variables. J Clin Endocrinol Metab 1988;67:1225–30.

(9) Suikkari AM, Sane T, Seppala M, Yki-Jarvinen H, Karonen SL, Koivisto VA. Prolonged exercise increases serum insulin-like growth factor-binding protein concentrations. J Clin Endocrinol Metab 1989;68:141–4.

(10) Batch JA, Baxter RC, Werther G. Abnormal regulation of insulin-like growth factor binding proteins in adolescents with insulin-dependent diabetes. J Clin Endocrinol Metab 1991;73:964–8.

(11) Brismar K, Gutniak M, Povoa G, Werner S, Hall K. Insulin regulates the 35 kDa IGF binding protein in patients with diabetes mellitus. J Endocrinol Invest 1988;11:599–602.

(12) Suikkari AM, Koivisto VA, Rutanen EM, Yki-Jarvinen H, Karonen SL, Seppala M. Insulin regulates the serum levels of low molecular weight insulin-like growth factor-binding protein. J Clin Endocrinol Metab 1988;66:266–72.

(13) Manousos O, Souglakos J, Bosetti C, Tzonou A, Chatzidakis V, Trichopoulos D, et al. IGF-I and IGF-II in relation to colorectal cancer. Int J Cancer 1999;83:15–7.

(14) Chan JM, Stampfer MJ, Giovannucci E, Gann PH, Ma J, Wilkinson P, et al. Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. Science 1998;279:563–6.

(15) Hsing AW, Chua S Jr, Gao YT, Gentzschein E, Chang L, Deng J, et al. Prostate cancer risk and serum levels of insulin and leptin: a population-based study. J Natl Cancer Inst 2001;93:783–9.

(16) Schaid DJ, McDonnell SK, Blute ML, Thibodeau SN. Evidence for autosomal dominant inheritance of prostate cancer. Am J Hum Genet 1998;62:1425–38.

(17) Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Willett WC. Height, body weight, and risk of prostate cancer. Cancer Epidemiol Biomarkers Prev 1997;6:557–63.

(18) Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC. Validity of self-reported waist and hip circumferences in men and women. Epidemiology 1990;1:466–73.

(19) Rimm EB, Giovannucci E, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. Am J Epidemiol 1992;135:1114–26.

(20) Chasan-Taber S, Rimm EB, Stampfer MJ, Spiegelman D, Colditz GA, Giovannucci E, et al. Reproducibility and validity of a self-administered physical activity questionnaire for male health professionals. Epidemiology 1996;7:81–6.

(21) Giovannucci E. Nutritional and environmental epidemiology of prostate cancer. In: Kantoff PW, Carroll PR, D'Amico AV, editors. Prostate cancer: principles and practice. Philadelphia (PA): Lippincott, Williams & Wilkins; 2002. p. 117–39.

(22) Narod S. Genetic epidemiology of prostate cancer. Biochim Biophys Acta 1999;1423:F1–13.

(23) Pasquali R, Casimirri F, Cantobelli S, Melchionda N, Morselli Labate AM, Fabbri R, et al. Effect of obesity and body fat distribution on sex hormones and insulin in men. Metabolism 1991;40:101–4.

(24) Barrett-Connor E, Kwat KT. Cigarette smoking and increased endogenous estrogen levels in men. Am J Epidemiol 1987;126:187–92.

(25) Dai WS, Gutain JP, Kuller LH, Cauley JA. Cigarette smoking and serum sex hormones in men. Am J Epidemiol 1988;128:796–805.

(26) Isidori AM, Caprio M, Strollo F, Moretti C, Frajese G, Isidori A, et al. Leptin and androgens in male obesity: evidence for leptin contribution to reduced androgen levels. J Clin Endocrinol Metab 1999;84:3673–80.

(27) Kazemi-Esfarjani P, Trifiro MA, Pinsky L. Evidence for a repressive function of the long polyglutamine tract in the human androgen receptor: possible pathogenetic relevance for the (CAG)n-expanded neuropathies. Hum Mol Genet 1995;4:523–7.

(28) Giovannucci E. Is the androgen receptor CAG repeat length significant for prostate cancer? Cancer Epidemiol Biomarkers Prev 2002;11(10 Pt 1):985–6.

NOTES