Body Size and Risk of Prostate Cancer in the European Prospective Investigation into Cancer and Nutrition

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Abstract

Background: **Body size has been hypothesized to influence the risk of prostate cancer; however, most epidemiologic studies have relied on body mass index (BMI) to assess adiposity, whereas only a few studies have examined whether body fat distribution predicts prostate cancer.**

Methods: **We examined the association of height, BMI, waist and hip circumference, and waist-hip ratio with prostate cancer risk among 129,502 men without cancer at baseline from 8 countries of the European Prospective Investigation into Cancer and Nutrition (EPIC), using Cox regression, with age as time metric, stratifying by study center and age at recruitment, and adjusting for education, smoking status, alcohol consumption, and physical activity.**

Results: **During a mean follow-up of 8.5 years, 2,446 men developed prostate cancer. Waist circumference and waist-hip ratio were positively associated with risk of advanced disease. The relative risk of advanced prostate cancer was 1.06 (95% confidence interval, 1.01-1.1) per 5-cm-higher waist circumference and 1.21 (95% confidence interval, 1.04-1.39) per 0.1-unit-higher waist-hip ratio. When stratified by BMI, waist circumference and waist-hip ratio were positively related to risk of total, advanced, and high-grade prostate cancer among men with lower but not among those with higher BMI ($P_{interaction}$ for waist with BMI, 0.25, 0.02, and 0.05, respectively; $P_{interaction}$ for waist-hip ratio with BMI, 0.27, 0.22, and 0.14; respectively).**

Conclusions: **These data suggest that abdominal adiposity may be associated with an increased risk of advanced prostate cancer. This association may be stronger among individuals with lower BMI; however, this finding needs confirmation in future studies.** (Cancer Epidemiol Biomarkers Prev 2008;17(11):3252–61)

Introduction

Today, prostate cancer is the most common cancer diagnosed in European men, and it is the third most common cause of cancer mortality in males in Europe. The etiology of the disease, however, remains poorly understood, and only a few risk factors have thus far been established, including age, family history of prostate cancer, and ethnicity (1). Body size has long been hypothesized to influence the risk of prostate cancer. However, most epidemiologic studies have failed to show overall significant associations between the body mass index (BMI, weight in kilograms divided by the square of the height in meters)—a measure of general adiposity—and risk of prostate cancer (2). Nevertheless, a recent meta-analysis suggested a weak positive association, with an estimated relative risk of prostate cancer of 1.05 [95% confidence interval (95% CI), 1.01-1.08] per 5 kg/m^2 (3). Some studies have suggested that when separated by stage of disease or by tumor grade, obesity

may be more strongly related to a higher risk of advanced stage prostate cancer or of high-grade tumors but not—or even inversely—to early stage (i.e., localized) prostate cancer or to low-grade tumors, but findings have been inconsistent (3-6). The association of waist circumference or waist-hip ratio (WHR), as measures of abdominal obesity, with risk of prostate cancer has been examined in only a few studies (3, 7–11), with most studies finding no significant associations.

Therefore, the aim of this study was to examine the association of anthropometric measures, including height, BMI, waist and hip circumference, and WHR, with risk of prostate cancer in participants of the European Prospective Investigation into Cancer and Nutrition (EPIC), a large European cohort study.

Subjects and Methods

Study Population. The 153,457 male participants in EPIC were ages 25 to 70 y at time of enrollment (1992-2000) and recruited from 19 centers in 8 European countries (Denmark, Germany, Greece, Italy, the Netherlands, Spain, Sweden, and the United Kingdom) predominantly from the general population residing in a given geographic area (i.e., town or province). Individuals provided written informed consent; completed questionnaires on diet, lifestyle, and medical history; and had anthropometric measurements taken (12, 13). Approval was obtained from the ethical review boards of the IARC and from all local institutions where participants had been recruited.

The present study is based on 148,372 men without prevalent cancer at any site at baseline, based on the self-reported questionnaire or based on information from the cancer registries. The male Umea, Sweden cohort (n = 12,289) was excluded because participants did not provide information on leisure time physical activity that was compatible with the other EPIC questionnaires and because waist and hip circumferences were not assessed at baseline. In addition, we excluded 3,332 men without height or weight measurements and 3,249 participants who had missing questionnaire data or—to reduce the effect on the analysis of implausible extreme values—who were in the top or bottom 1% of the ratio of energy intake to estimated energy requirement that was calculated from height, weight, gender, and age (14). Therefore, the study included a total of 129,502 participants.

Assessment of Endpoints. Incident prostate cancer case patients were identified by population cancer registries (Denmark, Italy, the Netherlands, Spain, Sweden, the United Kingdom) or by active follow-up (Germany and Greece), depending on the follow-up system in each of the participating centers. Active follow-up used a combination of methods, including health insurance records, cancer and pathology registries, and direct contact with participants or next of kin. Mortality data were also obtained from cancer or mortality registries at the regional or national level. Loss-to-follow up (defined as unknown vital status at the time of last follow-up) was generally lower than 6% in EPIC centers. Follow-up began at the date of enrollment and ended at either the date of diagnosis of prostate cancer, death, or last complete follow-up. Mortality data were coded following the guidelines from the 10th revision of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD-10), and cancer incidence data were coded according to the 2nd revision of the International Classification of Diseases for Oncology (ICD-O-2). We included all patients with prostate cancer (C61).

Data on the stage and grade of disease at diagnosis were collected from each center, where possible. The sources of this information varied between individual cases and between centers and included both clinical and surgical staging and grade information from both biopsies and prostatectomies. When data were available from more than one source, the most advanced stage or highest grade was used to categorize individuals. However, for most cases, we were unable to determine whether these data were derived from clinical or pathologic records. Prostate cancer was classified as localized [tumor-node-metastasis (TNM) staging score of T_0-T_2 and N_0/N_X and M_0, or stage coded in the recruitment center as localized] or advanced stage (T_3-T_4 and/or N_1-N_3 and/or M_1, or stage coded in the recruitment center as metastatic), and as low-grade (Gleason score of <7 or cases coded as well-differentiated or moderately differentiated) or high-grade tumors (Gleason scores of 7+ or cases coded as poorly differentiated or undifferentiated). In sensitivity analyses, we repeated our analysis with low-grade disease defined as Gleason score of <8 or equivalent, and high-grade disease defined as Gleason score of 8+ or equivalent.

Assessment of Anthropometric Data, Diet, and Lifestyle Factors. Weight and height were measured with subjects wearing no shoes (15). Depending on study center, waist circumference was measured either at the narrowest torso circumference, at the midpoint between the lower ribs and iliac crest, or by a combination of methods, whereby waist circumference was measured at the narrowest torso circumference, or, if it could not be identified, midway between the lower ribs and the iliac crest. Hip circumference was measured horizontally at the level of the largest lateral extension of the hips, or over the buttocks. The participants' body weights and waist and hip circumferences were corrected to reduce heterogeneity due to protocol differences in clothing worn during measurement, as described in detail

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elsewhere (15). For part of the Oxford (United Kingdom) cohort where only self-reported data were available, linear regression models were used to adjust these values using age-specific values from subjects with both measured and self-reported body measures (15–17). Waist circumference, hip circumference, and WHR measurements were missing for 1,268 (0.98%), 3,555 (2.75%), and 3,574 (2.76%) participants, respectively, who were excluded for analyses on these variables. Information on sociodemographic and lifestyle characteristics, medical history, alcohol consumption, and physical activity was obtained from questionnaires at study entry (12, 18–20).

Statistical Analyses. The association between anthropometric variables and risk of prostate cancer was analyzed by calculating relative risk estimates as hazard ratios using Cox proportional hazards models. Age was used as the underlying time variable, with entry and exit time defined as the subject's age at recruitment and age of prostate cancer diagnosis or censoring, respectively. We also analyzed the association according to tumor stage (localized or advanced) and tumor grade (low grade or high grade). Men who developed the competing end point were censored at the time of occurrence of that end point, whereas prostate cancer cases with missing information on staging or grading were excluded from the respective analyses. Differences between localized and advanced disease (and between low grade and high grade) in the associations with anthropometric variables were analyzed using the data augmentation method described by Lunn and McNeil (21) by testing the significance of the interaction term between the anthropometric variable with type of event.

Subjects were grouped into quintiles on the basis of the anthropometric variables of the entire male cohort. We also did additional analyses by grouping participants into predefined well-established categories for BMI (<25, 25-<30, or ≥30 kg/m^2), waist circumference (<102 or ≥102 cm), and WHR (<0.95 or ≥0.95; ref. 22). Models were stratified by integers of age at recruitment and by study center to reduce sensitivity to any violations of the proportional hazards assumption (using the STRATA statement in PROC PHREG in SAS). We further adjusted the analysis for smoking status (never, past, current, or unknown), education (no school degree or primary school, technical or professional school, secondary school, university degree, or unknown), alcohol consumption (grams/d, continuous), and physical activity (inactive, moderately inactive, moderately active, active, missing). Analyses of BMI, waist and hip circumference, and WHR were also adjusted for body height (continuously). Although BMI by definition should be largely uncorrelated with height, we decided to also adjust BMI for height to improve the comparability and interpretation of results presented for the different body size variables. Models for waist circumference, hip circumference, and WHR were also adjusted for BMI (continuously). To test for linear trend across categories, we used the median anthropometric variable within quintiles as a continuous variable. In separate analyses, we included body size measures as continuous variables in the models to estimate the relative risk of prostate cancer per unit increase in each anthropometric variable. In addition, we examined the association of waist circumference and WHR with prostate cancer risk across BMI tertiles. We tested for heterogeneity between the country-specific relative risk estimates for the associations of body size measures with risk of prostate cancer using the heterogeneity statistical derived from the inverse variance method (23).

All P values presented are two tailed, and a P value of <0.05 was considered statistically significant. Analyses were done using SAS 9.1 (SAS Institute) and Review Manager 4.2 (Nordic Cochrane Centre, The Cochrane Collaboration, 2003).

Results

A total of 129,502 men were followed for an average 8.5 ± 2.0 years, for a total of 1,097,000 person-years (Table 1). Mean age at baseline was 52.8 years. During follow-up, 2,446 members of the cohort were diagnosed with prostate cancer. A total of 1,490 incident cases (60.9%) had information on TNM staging, or equivalent information available; of these, 991 (66.5%) were classified as localized and 499 (33.5%) were classified as advanced. The Gleason score (or equivalent information) was available for 1,421 cases (58.1%); of these, 841 (59.2%) were classified as low grade and 580 (40.8%) were classified as high grade. Individuals with higher compared with those with lower BMI were older, reported a higher alcohol consumption, had lower education, were more likely to be past smokers, and were less likely to be never and current smokers (Table 2). The age and center adjusted Pearson's partial correlation coefficients of BMI with waist circumference, hip circumference, and WHR were 0.85, 0.77, and 0.55, respectively (all $P < 0.0001$).

None of the anthropometric variables was significantly related to risk of total prostate cancer (Table 3). However, waist circumference and WHR were positively associated with risk of advanced disease. On a continuous scale, a 5-cm-higher waist circumference was related to a 1.06-fold (95% CI, 1.01-1.1) higher risk of advanced prostate cancer, whereas a 0.1-unit-higher WHR was related to a 1.21-fold (95% CI, 1.04-1.39) higher risk of advanced disease. These associations did not differ significantly across the different countries for waist circumference ($P_{heterogeneity} = 0.56$) or WHR ($P = 0.93$). BMI was positively related to advanced prostate cancer and to high-grade tumors, and it was inversely related to localized disease and to low-grade tumors, but only the inverse association with low-grade tumors was statistically significant (relative risk per 5 kg/m^2, 0.88; 95% CI, 0.79-0.98). The results for grading tended to be slightly stronger but remained of borderline significance when we defined low-grade as Gleason score of <8 or equivalent, and high-grade as ≥8 or equivalent.

When we used established risk categories for BMI, the relative risks of total prostate cancer for overweight and obese individuals compared with nonoverweight men were 1.00 (95% CI, 0.92-1.10) and 0.97 (95% CI, 0.85-1.10), respectively. For localized disease, these relative risks were 0.96 (95% CI, 0.83-1.11) and 0.91 (95% CI, 0.74-1.11); for advanced disease, 1.05 (95% CI, 0.86-1.29) and 1.09 (95% CI, 0.83-1.44); for low-grade tumors, 0.96 (95% CI, 0.82-1.12) and 0.87 (95% CI, 0.70-1.08); and for high-grade tumors, 1.09 (95% CI, 0.90-1.31) and 1.08 (95% CI, 0.83-1.41), respectively. The relative risk of men with a waist circumference ≥ versus <102 cm was 1.00 (95% CI,

Table 1. Cohort characteristics of men from the EPIC

Country	Cohort Size, *n*	Age, y, mean	Follow-up, years, mean	Person-years	Number of incident prostate cancer cases*				
					Total	Localized cancer†	Advanced cancer‡	Low-grade cancer§	High-grade cancer‖
Italy	13,875	50.2	8.6	119,064	144	27	30	58	30
Spain	14,987	50.7	10.3	154,471	207	144	23	121	44
UK	22,450	53.0	8.5	189,865	477	181	99	134	165
The Netherlands	9,781	43.2	8.4	81,977	60	11	30	45	14
Greece	10,548	52.9	7.0	73,625	40	17	9	16	8
Germany	21,337	52.4	8.2	175,062	418	237	93	211	95
Sweden	10,256	59.0	10.2	104,383	728	184	109	178	112
Denmark	26,268	56.6	7.6	198,553	372	190	106	78	112
Total	129,502	52.8	8.5	1,097,000	2,446	991	499	841	580

*The difference between the total number of prostate cancer cases and the sum of localized and advanced cases (or the sum of low-grade and high-grade cases) indicates the number of cases where information on staging (or grading) was missing.
†Localized cancer indicates TNM staging score of T_0-T_2 and N_0/N_X and M_0, or equivalent.
‡Advanced cancer indicates T_3-T_4 and/or N_1-N_3 and/or M_1, or equivalent.
§Low-grade cancer indicates Gleason score of <7 or equivalent.
‖High-grade cancer indicates Gleason scores of 7+ or equivalent.

0.91-1.10) for total prostate cancer, 1.00 (95% CI, 0.87-1.16) for localized prostate cancer, 1.12 (95% CI, 0.91-1.38) for advanced prostate cancer, 0.98 (95% CI, 0.83-1.15) for low-grade prostate cancer, and 1.13 (95% CI, 0.93-1.37) for high-grade prostate cancer. The relative risk of men with a WHR of ≥0.095 versus <0.95 was 1.06 (95% CI, 0.98-1.16) for total prostate cancer, 1.09 (95% CI, 0.96-1.24) for localized prostate cancer, 1.20 (95% CI, 1.00-1.44) for advanced prostate cancer, 1.11 (95% CI, 0.96-1.27) for low-grade prostate cancer, and 1.16 (95% CI, 0.98-1.38) for high-grade prostate cancer.

The results for BMI were not significantly different between men ages <60 or ≥60 years at baseline (data not shown). For waist circumference and WHR, the associations with advanced prostate cancer tended to be stronger among elderly men (relative risk per 5-cm-higher waist circumference, 1.08; 95% CI, 1.02-1.15; relative risk per 0.1-unit-higher WHR, 1.22; 95% CI, 1.01-1.47) than for younger men (relative risk per 5-cm-higher waist circumference, 1.02; 95% CI, 0.95-1.10; relative risk per 0.1 unit higher WHR, 1.21; 95% CI, 0.96-1.53); however, tests for interaction were statistically nonsignificant ($P = 0.14$ and $P = 0.97$ for the interaction of age with waist circumference and WHR, respectively).

After further adjustment for BMI, there were significant or borderline-significant associations of waist circumference with risk of total prostate cancer, localized, and advanced prostate cancer (Table 4). Waist-hip ratio was significantly related to advanced prostate cancer after further adjustment for BMI (Table 4). These

Table 2. Characteristics of male study participants by quintiles of BMI in the EPIC

	BMI quintile				
	1	2	3	4	5
BMI, kg/m^2 range	<23.6	23.6-25.3	25.4-27.0	27.1-29.3	≥29.4
Mean	22.0	24.6	26.3	28.2	32.0
N	25,901	25,894	25,907	25,900	25,900
Age, y, mean	50.3	52.6	53.3	53.8	54.0
Alcohol, g/d, mean	20.6	21.8	22.8	23.9	25.4
Smoking status, %					
Never	34.2	32.4	30.7	28.2	26.8
Past	29.5	35.7	38.7	40.8	41.7
Current	35.1	30.5	29.2	29.6	30.1
Weight, kg, mean	68.3	75.5	80.1	85.2	95.7
Height, cm, mean	175.9	175.2	174.5	173.8	172.8
Waist, cm, mean	83.7	89.7	93.8	98.4	107.4
Hip, cm, mean	94.2	97.9	100.3	103.0	108.8
Waist-hip ratio, mean	0.889	0.918	0.937	0.957	0.988
Education, %					
No school degree or primary school	21.7	24.7	28.5	35.5	42.4
Technical or professional school	24.3	25.2	25.7	25.3	23.7
Seconary school	15.7	16.0	15.2	13.8	12.8
University degree	34.7	30.9	27.4	22.6	17.9
Physical activity, %					
Inactive	19.9	20.6	20.3	20.0	19.9
Moderately inactive	29.0	28.2	28.4	28.8	29.1
Moderately active	35.5	35.0	35.5	35.4	36.1
Active	13.0	13.8	13.2	13.6	13.1

NOTE: All values except age, number of subjects, and BMI are standardized to the age-distribution of the male study population using 5-y categories. Percentages may not add up to 100% because of missing values.

Table 3. Relative risk and 95% CI of prostate cancer across quintiles of anthropometric measures among men in the EPICs

	Quintile									P_{trend}* statistic	Continuously†		P difference between end points‡
	1	2		3		4		5					
	RR	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI		RR	95% CI	
Height, cm	<168.0	168.0-172.4		172.5-176.1		176.2-180.4		≥180.5					
Total prostate cancer	1.00	0.98	0.87-1.12	0.97	0.85-1.10	0.97	0.85-1.11	1.04	0.91-1.20	0.65	1.01	0.98-1.04	—
Localized cancer§	1.00	1.08	0.89-1.31	1.06	0.87-1.29	0.94	0.76-1.17	1.08	0.86-1.35	0.88	1.01	0.96-1.06	0.98
Advanced cancer‖	1.00	0.93	0.70-1.23	0.96	0.72-1.27	1.04	0.78-1.39	0.97	0.71-1.33	0.88	1.01	0.94-1.08	
Low-grade cancer¶	1.00	1.03	0.84-1.26	0.87	0.70-1.08	0.86	0.68-1.08	0.94	0.73-1.19	0.26	0.98	0.93-1.03	0.46
High-grade cancer**	1.00	0.85	0.65-1.11	1.02	0.78-1.32	1.00	0.76-1.30	1.07	0.81-1.42	0.38	1.01	0.95-1.08	
BMI, kg/m^2	<23.6	23.6-25.3		25.4-27.0		27.1-29.3		≥29.4					
Total prostate cancer	1.00	1.06	0.93-1.20	1.08	0.95-1.23	0.95	0.83-1.09	0.99	0.86-1.13	0.37	0.96	0.90-1.02	—
Localized cancer§	1.00	1.09	0.89-1.34	1.02	0.83-1.25	0.88	0.71-1.10	0.95	0.77-1.18	0.22	0.92	0.84-1.01	0.03
Advanced cancer‖	1.00	1.05	0.78-1.40	1.25	0.94-1.66	1.08	0.81-1.46	1.17	0.86-1.58	0.34	1.09	0.96-1.24	
Low-grade cancer¶	1.00	0.97	0.78-1.21	0.95	0.77-1.19	0.83	0.66-1.04	0.84	0.66-1.06	0.06	0.88	0.79-0.98	0.04
High-grade cancer**	1.00	1.26	0.96-1.65	1.34	1.02-1.76	1.16	0.87-1.54	1.23	0.92-1.65	0.37	1.04	0.92-1.18	
Waist, cm	<86.0	86.0-91.8		91.9-96.5		96.6-102.9		≥103.0					
Total prostate cancer	1.00	1.00	0.88-1.15	0.98	0.86-1.13	1.03	0.90-1.18	0.99	0.86-1.14	0.99	1.00	0.97-1.02	—
Localized cancer§	1.00	1.00	0.80-1.25	0.98	0.79-1.22	1.05	0.84-1.30	0.98	0.78-1.22	0.89	0.99	0.96-1.03	0.03
Advanced cancer‖	1.00	1.15	0.85-1.57	1.05	0.77-1.44	1.29	0.95-1.75	1.30	0.96-1.77	0.07	1.06	1.01-1.11	
Low-grade cancer¶	1.00	0.87	0.69-1.10	0.85	0.68-1.08	1.05	0.84-1.31	0.87	0.69-1.10	0.65	0.98	0.94-1.01	0.05
High-grade cancer**	1.00	1.06	0.80-1.41	1.10	0.83-1.47	1.14	0.86-1.51	1.23	0.92-1.63	0.13	1.03	0.99-1.08	
Hip, cm	<95.2	95.2-98.9		99.0-101.9		102.0-105.9		≥106.0					
Total prostate cancer	1.00	0.93	0.82-1.06	0.97	0.86-1.10	1.03	0.90-1.17	0.91	0.79-1.05	0.47	0.98	0.95-1.01	—
Localized cancer§	1.00	0.98	0.79-1.22	1.01	0.83-1.24	1.02	0.82-1.27	0.96	0.77-1.20	0.80	0.99	0.94-1.04	0.18
Advanced cancer‖	1.00	1.07	0.80-1.44	1.05	0.79-1.39	1.26	0.93-1.69	1.19	0.87-1.62	0.18	1.05	0.98-1.12	
Low-grade cancer¶	1.00	0.94	0.75-1.18	0.97	0.78-1.20	1.06	0.84-1.33	0.85	0.67-1.09	0.37	0.96	0.91-1.02	0.12
High-grade cancer**	1.00	0.99	0.75-1.32	1.11	0.85-1.45	1.32	1.00-1.74	1.13	0.84-1.52	0.16	1.03	0.96-1.10	
WHR	<0.887	0.887-0.922		0.923-0.952		0.953-0.989		≥0.990					
Total prostate cancer	1.00	0.96	0.84-1.10	0.89	0.78-1.02	1.03	0.90-1.18	1.01	0.88-1.15	0.53	1.02	0.95-1.10	—
Localized cancer§	1.00	0.90	0.73-1.12	0.81	0.65-1.01	0.99	0.80-1.22	0.92	0.75-1.14	0.88	0.99	0.89-1.10	0.02
Advanced cancer‖	1.00	1.25	0.90-1.73	1.21	0.87-1.68	1.39	1.01-1.91	1.43	1.04-1.97	0.03	1.21	1.04-1.39	
Low-grade cancer¶	1.00	0.94	0.75-1.18	0.77	0.61-0.98	1.04	0.83-1.30	0.92	0.73-1.16	0.87	0.97	0.86-1.09	0.13
High-grade cancer**	1.00	0.81	0.61-1.08	0.86	0.65-1.14	1.02	0.78-1.34	1.03	0.78-1.35	0.33	1.11	0.97-1.28	

NOTE: Multivariable adjusted relative risk for height is derived from Cox regression using age as the underlying time variable, and stratified by center and age at recruitment with additional adjustment for smoking status (never, past, current, or unknown), education (no school degree or primary school, technical or professional school, secondary school, university degree, or unknown), alcohol intake (continuously), and physical activity (inactive, moderately inactive, moderately active, active, or missing). Multivariable model for BMI, weight, waist, hip, and WHR are further adjusted for height (continuously).

Abbreviation: RR, relative risk.

*P_{trend} (two sided) across categories is based on the median anthropometric variable within quintiles as a continuous variable and was calculated using the Wald χ^2 statistic.

†Relative risk estimated per x unit increase in anthropometric variables, where x = 5 cm for height, x = 5 kg/m^2 for BMI, x = 5 cm for waist, x = 5 cm for hip, and x = 0.1 for WHR.

‡P value for difference between associations of anthropometry with end points (localized versus advanced, or low grade versus high grade) obtained from the interaction terms of anthropometric variables (continuously) with type of events obtained using the data augmentation method (Lunn et al., 1995.). Interaction terms between each covariate with type of outcome were also included in each model to allow for differences in associations of covariates with the different outcomes.

§Localized cancer indicates TNM staging score of T_0-T_2 and N_0/N_X and M_0, or equivalent.

‖Advanced cancer indicates T_3-T_4 and/or N_1-N_3 and/or M_1, or equivalent.

¶Low-grade cancer indicates Gleason score of <7 or equivalent.

**High-grade cancer indicates Gleason scores of 7+ or equivalent.

associations did not differ significantly between younger and elderly men.

When we examined the associations within strata defined by tertiles of BMI, we found positive associations with risk of total prostate cancer, advanced prostate cancer, and high-grade prostate cancer for waist circumference and WHR among men with lower BMI levels (<24.9) but not among men with intermediary (24.9 to <27.8) or higher BMI levels (≥27.8; $P_{interaction}$ of waist circumference and WHR with BMI, P = 0.25 and P = 0.27, respectively, for total prostate cancer; P = 0.02 and P = 0.22, respectively, for advanced prostate cancer; and P = 0.05 and P = 0.14, respectively, for high-grade prostate cancer; Table 5). Upon cross-classification, men in the lowest tertile of BMI and in the highest tertile of waist circumference or WHR had the highest risk of total prostate cancer (Fig. 1), advanced prostate cancer, and high-grade prostate cancer (data not shown) when compared with men in the lowest tertile of BMI and in the lowest tertile of waist circumference or WHR. When we excluded from the analysis person-time and incident events from the first 5 years of follow-up, the results did not appreciably change but became slightly stronger (data not shown).

Discussion

In this large prospective cohort, waist circumference and WHR, as indicators of abdominal adiposity, were

positively related to risk of advanced prostate cancer. In stratified analyses, higher levels of waist circumference or WHR were associated with increased risks of total prostate cancer, advanced prostate cancer, and high-grade prostate cancer among individuals with lower BMI but not among men with higher BMI levels. These data suggest that the association of abdominal adiposity with risk of prostate cancer may differ according to body mass.

Most previous studies found no significant association between BMI and risk of total prostate cancer, which is in agreement with our findings (3). Some studies suggested stronger positive associations for advanced prostate cancer compared with localized disease, although in the majority of studies, these associations were not statistically significant. In a meta-analysis by MacInnis et al. (3), the estimated relative risk per 5 kg/m^2 was 1.12 (95% CI, 1.01-1.23) for advanced prostate cancer, which is consistent with the relative risk estimate of 1.09 observed in our study. Two more recent cohort studies suggested that the association of BMI with risk of prostate cancer may also differ by grading of the tumor, with positive associations for high-grade cancer and inverse associations for low-grade disease (4, 5). Accordingly, in our analysis, BMI tended to be positively associated with high-grade tumors and inversely related to low-grade tumors. More recent studies also suggested that BMI may be more strongly related to prostate cancer mortality than to prostate cancer incidence (5, 6, 24). Fatal prostate cancer may reflect more aggressive tumor behavior; however, in a previous analysis, we found no significant association of BMI with prostate cancer mortality (25). Data from the Health Professionals Follow-up Study suggested that the association of BMI with risk of prostate cancer may depend on age with inverse associations among younger men but nonsignificant association among the elderly (9); however, in our analysis, no such interaction was observed.

Fewer studies have examined the association of abdominal adiposity with risk of prostate cancer, and in most of these studies, waist circumference, hip circumference or WHR were not significantly related to total prostate cancer (3, 8, 10, 11, 26–31), which is in agreement with our findings. Only very few studies reported results for waist circumference or WHR by stage or grade of disease (11, 26, 27). In the Health Professionals Follow-up Study, self-reported waist circumference, hip circumference, and WHR were not significantly related to advanced prostate cancer (26). In the Melbourne Collaborative Cohort Study, waist circumference was significantly positively associated with risk of aggressive prostate cancer (27). In a population-based case-control study in China, waist circumference was not related to advanced stage prostate cancer; however, that study found significant inverse associations of

Table 4. Relative risk and 95% CI of prostate cancer across quintiles of waist and hip circumference and WHR after further adjustment for BMI among men in the EPIC

	Quintile									P_{trend}* statistic	Continuously†		P difference between end points‡
	1	2		3		4		5					
	RR	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI		RR	95% CI	
Waist, cm	<86.0	86.0-91.8		91.9-96.5		96.6-102.9		≥103.0					
Total prostate cancer	1.00	1.06	0.92-1.22	1.08	0.93-1.26	1.18	0.99-1.40	1.23	0.99-1.54	0.045	1.04	1.00-1.09	—
Localized cancer§	1.00	1.10	0.87-1.39	1.15	0.90-1.48	1.32	1.00-1.74	1.43	1.00-2.03	0.03	1.08	1.01-1.16	0.59
Advanced cancer‖	1.00	1.16	0.84-1.60	1.06	0.75-1.51	1.32	0.90-1.93	1.34	0.83-2.17	0.22	1.11	1.02-1.22	
Low-grade cancer¶	1.00	0.99	0.77-1.27	1.05	0.81-1.37	1.43	1.07-1.92	1.43	0.98-2.09	0.02	1.06	0.98-1.14	0.73
High-grade cancer**	1.00	1.10	0.82-1.49	1.17	0.85-1.62	1.24	0.87-1.77	1.42	0.91-2.23	0.12	1.08	0.99-1.18	
Hip, cm	<95.2	95.2-98.9		99.0-101.9		102.0-105.9		≥106.0					
Total prostate cancer	1.00	0.96	0.84-1.10	1.02	0.89-1.18	1.11	0.94-1.31	1.03	0.83-1.27	0.46	1.00	0.94-1.06	—
Localized cancer§	1.00	1.06	0.85-1.33	1.16	0.92-1.46	1.24	0.95-1.63	1.31	0.93-1.83	0.09	1.08	0.99-1.18	0.42
Advanced cancer‖	1.00	1.05	0.77-1.42	1.01	0.73-1.39	1.18	0.82-1.71	1.08	0.68-1.72	0.65	1.01	0.89-1.15	
Low-grade cancer¶	1.00	1.03	0.81-1.31	1.13	0.88-1.44	1.32	0.99-1.76	1.20	0.83-1.74	0.18	1.05	0.95-1.15	0.81
High-grade cancer**	1.00	1.01	0.76-1.36	1.15	0.86-1.56	1.40	0.99-1.97	1.24	0.80-1.92	0.18	1.03	0.92-1.15	
WHR	<0.887	0.887-0.922		0.923-0.952		0.953-0.989		≥0.990					
Total prostate cancer	1.00	0.99	0.86-1.13	0.93	0.81-1.07	1.09	0.95-1.26	1.10	0.94-1.29	0.09	1.08	0.99-1.17	—
Localized cancer§	1.00	0.94	0.75-1.17	0.86	0.68-1.07	1.07	0.85-1.33	1.04	0.81-1.33	0.39	1.06	0.93-1.20	0.22
Advanced cancer‖	1.00	1.24	0.89-1.73	1.20	0.86-1.68	1.37	0.98-1.92	1.40	0.97-2.01	0.07	1.20	1.01-1.42	
Low-grade cancer¶	1.00	0.99	0.78-1.25	0.84	0.65-1.07	1.16	0.92-1.48	1.10	0.84-1.44	0.23	1.06	0.92-1.21	0.60
High-grade cancer**	1.00	0.81	0.60-1.08	0.85	0.64-1.14	1.01	0.76-1.35	1.01	0.73-1.38	0.47	1.12	0.95-1.32	

NOTE: Relative risks are derived from Cox regression using age as the underlying time variable, stratified by center and age at recruitment, and further adjustment for smoking status (never, past, current, or unknown), education (no school degree or primary school, technical or professional school, secondary school, university degree, or unknown), alcohol intake (continuously), physical activity (inactive, moderately inactive, moderately active, active, or missing), height (continuously), and BMI (continuously).

*P_{trend} (two sided) across categories is based on the median anthropometric variable within quintiles as a continuous variable and was calculated using the Wald χ^2 statistic.

†RR estimated per x unit increase in anthropometric variables, where x = 5 cm for waist, x = 5 cm for hip, and x = 0.1 for WHR.

‡P value for difference between associations of anthropometry with end points (localized versus advanced, or low grade versus high grade) obtained from the interaction terms of anthropometric variables (continuously) with type of events obtained using the data augmentation method (Lunn et al., 1995). Interaction terms between each covariate with type of outcome were also included in each model to allow for differences in associations of covariates with the different outcomes.

§Localized cancer indicates TNM staging score of T_0-T_2 and N_0/N_X and M_0, or equivalent.

‖Advanced cancer indicates T_3-T_4 and/or N_1-N_3 and/or M_1, or equivalent.

¶Low-grade cancer indicates Gleason score of <7 or equivalent.

**High-grade cancer indicates Gleason scores of 7+ or equivalent.

hip circumference with total prostate cancer and with advanced disease, and significant positive associations of WHR with total, localized, and advanced prostate cancer (11). In our analysis, waist circumference and WHR were both positively related to risk of advanced prostate cancer. This is in line with our prior observation that waist circumference and WHR were positively related to prostate cancer mortality (25).

Table 5. Relative risk and 95% CI of prostate cancer according to tertiles of waist circumference and WHR within strata of BMI among men in the EPIC

	Tertile												P_{trend}** statistic	Continuously ††		P difference between end points ‡‡
	1			2				3								
	*n**	*N* †	RR	*n**	*N* †	RR	95%, CI	*n**	*N* †	RR	95%, CI			RR	95%, CI	
Waist	<90.0			90.0-<98.0				≥98.0								
BMI, <24.9																
Total prostate cancer	523	31,602	1.00	246	10,415	1.11	0.94-1.31	26	721	1.67	1.10-2.53	0.03		1.03	0.97-1.10	—
Localized cancer ‡	198	31,368	1.00	90	10,314	1.02	0.78-1.33	9	716	1.34	0.67-2.69	0.60		1.01	0.92-1.13	0.01
Advanced cancer§	91	31,368	1.00	55	10,314	1.41	0.99-2.03	12	716	3.87	1.96-7.63	0.0005		1.29	1.11-1.49	
Low-grade cancer‖	170	31,355	1.00	74	10,304	1.07	0.80-1.43	6	713	1.23	0.53-2.87	0.56		0.96	0.86-1.08	0.04
High-grade cancer¶	106	31,355	1.00	61	10,304	1.42	1.01-1.99	12	713	3.87	1.99-7.51	0.0003		1.18	1.02-1.35	
BMI, 24.9-<27.8																
Total prostate cancer	154	8,971	1.00	494	25,095	0.85	0.70-1.03	237	8,683	1.03	0.82-1.29	0.44		1.01	0.94-1.08	—
Localized cancer ‡	54	8,906	1.00	208	24,899	0.95	0.69-1.30	98	8,596	1.06	0.74-1.54	0.60		1.05	0.94-1.17	0.82
Advanced cancer§	35	8,906	1.00	90	24,899	0.74	0.49-1.11	52	8,596	1.12	0.69-1.82	0.39		1.07	0.93-1.24	
Low-grade cancer‖	50	8,906	1.00	172	24,887	0.95	0.68-1.32	89	8,594	1.25	0.85-1.84	0.15		1.07	0.95-1.19	0.57
High-grade cancer¶	39	8,906	1.00	114	24,887	0.77	0.53-1.13	59	8,594	1.01	0.64-1.59	0.69		1.00	0.87-1.16	
BMI, ≥27.8																
Total prostate cancer	9	689	1.00	118	8,962	0.74	0.37-1.47	630	33,096	0.87	0.44-1.72	0.20		1.02	0.97-1.07	—
Localized cancer ‡	1	682	1.00	54	8,916	2.41	0.33-17.55	277	32,885	2.58	0.36-18.56	0.45		1.03	0.96-1.10	0.29
Advanced cancer§	1	682	1.00	18	8,916	1.25	0.16-9.48	142	32,885	2.17	0.29-15.97	0.03		1.09	0.99-1.20	
Low-grade cancer‖	2	684	1.00	41	8,912	1.10	0.26-4.61	233	32,856	1.45	0.35-5.95	0.11		0.98	0.90-1.07	0.12
High-grade cancer¶	2	684	1.00	27	8,912	0.78	0.18-3.37	157	32,856	1.08	0.25-4.59	0.18		1.07	0.97-1.18	
WHR	<0.911			0.911-<0.963				≥0.963								
BMI, <24.9																
Total prostate cancer	422	25,292	1.00	250	11,706	0.98	0.83-1.15	120	4,372	1.31	1.06-1.62	0.058		1.15	0.99-1.32	—
Localized cancer ‡	167	25,108	1.00	87	11,596	0.83	0.63-1.08	43	4,328	1.07	0.76-1.52	0.81		1.02	0.81-1.28	0.004
Advanced cancer§	71	25,108	1.00	53	11,596	1.24	0.86-1.79	33	4,328	1.85	1.19-2.87	0.008		1.68	1.23-2.30	
Low-grade cancer‖	149	25,107	1.00	67	11,580	0.77	0.57-1.03	33	4,318	1.05	0.71-1.56	0.59		0.99	0.77-1.28	0.08
High-grade cancer¶	88	25,107	1.00	57	11,580	1.17	0.83-1.65	33	4,318	1.77	1.16-2.71	0.01		1.37	1.04-1.81	
BMI, 24.9-<27.8																
Total prostate cancer	217	12,621	1.00	372	17,212	0.95	0.80-1.12	294	12,304	0.98	0.82-1.18	0.91		0.99	0.86-1.14	—
Localized cancer ‡	90	12,536	1.00	135	17,050	0.81	0.62-1.07	135	12,204	1.05	0.79-1.38	0.54		1.07	0.86-1.33	0.89
Advanced cancer§	42	12,536	1.00	75	17,050	0.99	0.67-1.46	59	12,204	0.96	0.64-1.46	0.85		1.04	0.76-1.41	
Low-grade cancer‖	74	12,534	1.00	123	17,056	0.94	0.70-1.26	114	12,186	1.16	0.85-1.58	0.27		1.12	0.89-1.41	0.25
High-grade cancer¶	56	12,534	1.00	93	17,056	0.90	0.64-1.26	62	12,186	0.78	0.53-1.13	0.19		0.89	0.66-1.19	
BMI, ≥27.8																
Total prostate cancer	66	4,196	1.00	198	12,966	0.83	0.63-1.10	490	25,259	0.96	0.73-1.25	0.51		1.08	0.94-1.24	—
Localized cancer ‡	26	4,168	1.00	93	12,899	0.99	0.64-1.54	213	25,093	1.05	0.69-1.60	0.67		1.04	0.85-1.27	0.29
Advanced cancer§	12	4,168	1.00	38	12,899	0.86	0.45-1.67	111	25,093	1.05	0.57-1.94	0.49		1.25	0.93-1.68	
Low-grade cancer‖	26	4,168	1.00	77	12,892	0.84	0.53-1.33	173	25,069	0.91	0.59-1.41	0.99		0.95	0.76-1.20	0.11
High-grade cancer¶	12	4,168	1.00	47	12,892	1.11	0.58-2.11	127	25,069	1.41	0.76-2.60	0.12		1.25	0.96-1.63	

NOTE: Relative risk is derived from Cox regression using age as the underlying time variable, and stratified by center and age at recruitment with further adjustment smoking status (never, past, current, or unknown), education (no school degree or primary school, technical or professional school, secondary school, university degree, or unknown), alcohol intake (continuously), physical activity (inactive, moderately inactive, moderately active, active, or missing), and height (continuously).

The P values for the tests of interaction between BMI and waist circumference (based on the likelihood ratio test for the comparison of a model with interaction term [waist × BMI] to a model without interaction term with 4 degrees of freedom) were $P = 0.25$ for total prostate cancer, $P = 0.82$ for localized cancer, $P = 0.02$ for advanced cancer, $P = 0.99$ for low-grade cancer, and $P = 0.05$ for high-grade cancer. For WHR these P values were $P = 0.27$ for total prostate cancer, $P = 0.91$ for localized cancer, $P = 0.22$ for advanced cancer, $P = 0.70$ for low-grade cancer, and $P = 0.14$ for high-grade cancer.

*Number of incident cases.

†Total number of individuals.

‡Localized cancer indicates TNM staging score of T_0-T_2 and N_0/N_X and M_0, or equivalent.

§Advanced cancer indicates T_3-T_4 and/or N_1-N_3 and/or M_1, or equivalent.

‖Low-grade cancer indicates Gleason score of <7 or equivalent.

¶High-grade cancer indicates Gleason scores 7+ or equivalent.

**P_{trend} (two sided) across categories is based on the median anthropometric variable within quintiles as a continuous variable and was calculated using the Wald χ^2 statistic.

†† RR estimated per x unit increase in anthropometric variables, where $x = 5$ cm for waist and $x = 0.1$ for WHR.

‡‡ P value for difference between associations of anthropometry with end points (localized versus advanced, or low grade versus high grade) obtained from the interaction terms of anthropometric variables (continuously) with type of events obtained using the data augmentation method (Lunn et al., 1995). Interaction terms between each covariate with type of outcome were also included in each model to allow for differences in associations of covariates with the different outcomes.

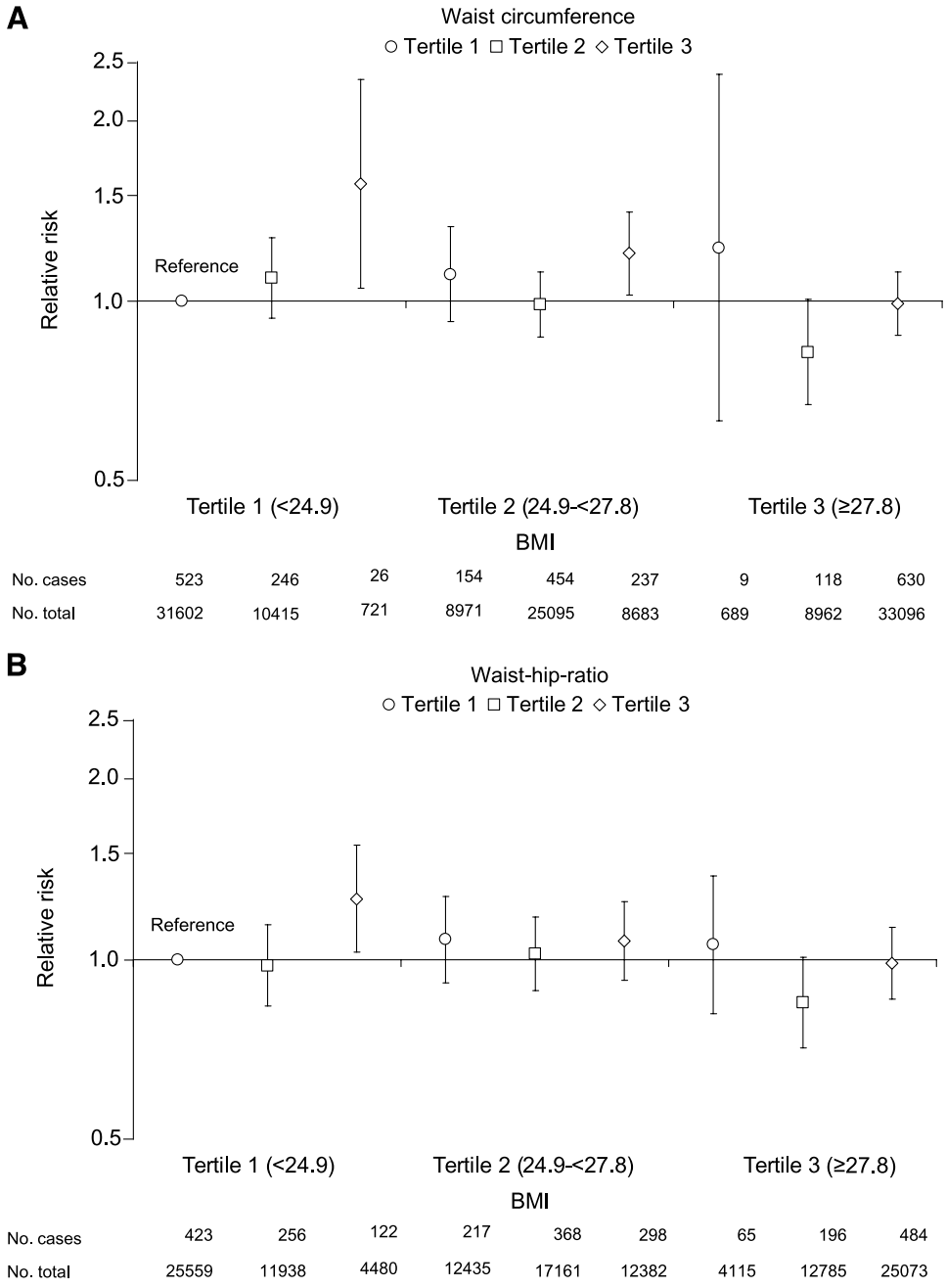

Figure 1. Multivariable adjusted relative risk of total prostate cancer according to tertiles of BMI and tertiles of waist circumference (**A**) or WHR (**B**), respectively. *Symbols,* relative risks; *error bars,* 95% confidence intervals. The reference category represents individuals in the lowest tertile of BMI and the lowest tertile of waist circumference or WHR, respectively. The multivariable adjusted relative risk were derived from Cox regression using age as the underlying time variable, and stratified by center and age at recruitment with additional adjustment for smoking status, education, alcohol intake, physical activity, and height. Note that the relative risks (*Y*-axis) are plotted on a logarithmic scale.

Waist circumference and BMI are highly correlated and—when considered individually—reflect the extent of both abdominal and general obesity. To estimate the effect of abdominal adiposity on risk of prostate cancer independent of general obesity, we adjusted waist circumference for BMI, and we also examined the association of waist circumference with prostate cancer risk within BMI strata. We found suggestive positive associations of waist circumference and WHR with total prostate cancer, advanced prostate cancer, and high-grade prostate cancer among men with lower BMI but not among those with intermediate or higher BMI. When cross-classified, men with the lowest BMI and the highest waist circumference or WHR had the highest relative risk of prostate cancer. It is tempting to speculate whether the potential interaction between general and abdominal adiposity is among the reasons why previous studies did not find significant associations for waist circumference or WHR with prostate cancer risk across the entire range of BMI. Alternatively, our finding may also reflect the play of chance, given that we did multiple subgroup analyses and given that the number of individuals in discordant categories was low, particularly for waist circumference and BMI.

The mechanisms that may link abdominal adiposity with risk of advanced prostate cancer are unclear. Obese men have increased serum estradiol levels but decreased testosterone levels compared with nonobese

men. Interestingly, in a subsample of EPIC, we found that men with the lowest BMI and the highest waist circumference or WHR had the lowest serum androgens levels.[29] Androgens are required for the growth, maturation, and differentiation of the prostatic gland (32, 33). It was thus suggested that testosterone may promote prostate tumor development but also help maintain prostate tumor differentiation (34), which may explain why obese individuals with low testosterone levels have a higher risk of developing undifferentiated tumors (35, 36). However, most prospective studies found no significant associations of androgens levels with risk of prostate cancer (37). Other mechanisms that may link abdominal obesity with prostate cancer may include high circulating concentrations of insulin, bioavailable insulin-like growth factor I, or leptin, or low adiponectin levels, although prospective studies on this topic have provided inconsistent results (38–48). Alternatively, or additionally, the fact that abdominally obese individuals may have a higher risk of advanced prostate cancer but a lower risk of early stage disease might be partly explained by delayed detection and diagnosis of prostate cancer in obese individuals (35, 36). Proposed reasons for difficulties in prostate cancer detection in obese individuals include lower prostate-specific antigen levels or less frequent prostate-specific antigen testing, as well as the possibility that a digital rectal examination and evaluation of the prostate gland may be more difficult to perform in obese men (35, 36). However, this does not easily explain the observation that abdominal adiposity was related to increased prostate cancer risk among men with lower BMI but not among men with higher BMI.

It has been suggested that height may be related to an increased risk of prostate cancer as it may reflect exposure to insulin and insulin-like growth factor I in preadulthood (49). A meta-analysis of 39 case-control and cohort studies suggested a weak positive association (relative risk of 1.05; 95% CI, 1.02-1.09; per 10 cm; ref. 3), although the majority of studies found no significant association, which is in agreement with our findings.

A potential limitation of our analysis is that the combination of related measures may lead to imprecision and instability of the risk estimates. However, the width of the confidence intervals did not substantially change when waist circumference or WHR were adjusted for BMI, therefore indicating that these combinations did not substantially decrease precision. Nevertheless, the number of individuals was low in discordant categories of BMI and waist circumference, thus limiting the precision of relative risk estimates for the cross-classified analysis, which therefore need to be interpreted cautiously. However, the cross-classification based on WHR and BMI provided more robust results that mirrored those for waist circumference.

The EPIC core questionnaire on physical activity was shown to be suitable for ranking subjects according to their physical activity level but may be less suitable for estimating energy expenditure at an absolute level (50). Nevertheless, physical activity—as assessed by the EPIC core questionnaire—was inversely related to risk of colon cancer (20), supporting its use to control for potential confounding.

[29] Allen N, Key T, unpublished observations.

Although we excluded men with a history of cancer at baseline, our study may include men with underlying but undiagnosed cancer, and weight loss as observed in advanced metastasized tumors may have preferentially lead to a reduction in lean body mass with smaller effects on abdominal fat depots in these individuals. However, weight loss is an uncommon clinical feature of prostate cancer and is therefore unlikely to fully explain the higher risk of prostate cancer in men with low BMI and high waist circumference. Furthermore, the strength of the associations did not change when we excluded men who developed prostate cancer within the first 5 years of follow-up. There were slight differences in the method of assessment of waist and hip circumference between centers in EPIC; however, we found similar results for the associations of body size with risk of prostate cancer across countries, which also reduces the possibility of residual confounding by geographic region.

In conclusion, results from this large prospective cohort suggest that abdominal adiposity may be related to risk of advanced prostate cancer. Furthermore, our results suggest that higher waist circumference or WHR may be associated with increased risks of total prostate cancer, advanced prostate cancer, and high-grade prostate cancer among individuals with lower BMI but not among men with higher BMI levels; however, these findings warrant confirmation in future studies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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