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BMC Medicine

RESEARCH ARTICLE

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Tall height and obesity are associated with an increased risk of aggressive prostate cancer: results from the EPIC cohort study

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Abstract

Background: The relationship between body size and prostate cancer risk, and in particular risk by tumour characteristics, is not clear because most studies have not differentiated between high-grade or advanced stage tumours, but rather have assessed risk with a combined category of aggressive disease. We investigated the association of height and adiposity with incidence of and death from prostate cancer in 141,896 men in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.

Methods: Multivariable-adjusted Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). After an average of 13.9 years of follow-up, there were 7024 incident prostate cancers and 934 prostate cancer deaths.

Results: Height was not associated with total prostate cancer risk. Subgroup analyses showed heterogeneity in the association with height by tumour grade ($P_{heterogeneity} = 0.002$), with a positive association with risk for high-grade but not low-intermediate-grade disease (HR for high-grade disease tallest versus shortest fifth of height, 1.54; 95% CI, 1.18–2.03). Greater height was also associated with a higher risk for prostate cancer death (HR = 1.43, 1.14–1.80). Body mass index (BMI) was significantly inversely associated with total prostate cancer, but there was evidence of heterogeneity by tumour grade ($P_{heterogeneity} = 0.01$; HR = 0.89, 0.79–0.99 for low-intermediate grade and HR = 1.32, 1.01–1.72 for high-grade prostate cancer) and stage ($P_{heterogeneity} = 0.01$; HR = 0.86, 0.75–0.99 for localised stage and HR = 1.11, 0.92–1.33 for advanced stage). BMI was positively associated with prostate cancer death (HR = 1.35, 1.09–1.68). The results for waist circumference were generally similar to those for BMI, but the associations were slightly stronger for high-grade (HR = 1.43, 1.07–1.92) and fatal prostate cancer (HR = 1.55, 1.23–1.96).

Conclusions: The findings from this large prospective study show that men who are taller and who have greater adiposity have an elevated risk of high-grade prostate cancer and prostate cancer death.

Keywords: Adiposity, Obesity, Height, Prostate cancer, Cohort study, Tumour characteristics, High grade

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Background

Prostate cancer is the most common cancer in men in Europe, and the second most frequently diagnosed cancer in men worldwide [1]. While relatively little is known about prostate cancer aetiology, hormones have been implicated; for example, circulating insulin-like growth factor I (IGF-I) concentrations are associated with prostate cancer risk [2]. A relatively large body size has been proposed to influence several metabolic and hormonal mechanisms that can promote cancer development [3]. With increasing global rates of overweight and obesity [4], the potential role of obesity in carcinogenesis has become a significant public health concern.

Several prospective studies have investigated the association of body size with the development of prostate cancer [3, 5–11]. The results have suggested differences in associations of body size with risk according to prostate tumour characteristics [12], but relatively few studies have investigated whether body size is related to a higher risk of clinically relevant aggressive prostate cancer [3, 7–9]. The latest World Cancer Research Fund meta-analysis reported that height was related to total prostate cancer and 'advanced' prostate cancer, including as 'advanced' prostate cancer various aggressive forms of the disease, but not differentiating between stage, grade and prostate cancer death because of the small number of available studies with data on these separate outcomes [12]. This meta-analysis also reported that obesity was associated with 'advanced' prostate cancer. The latest meta-analysis published in a peer-reviewed journal classified incident prostate cases into two categories ('localised' or 'advanced') using a combination of Gleason score, World Health Organization (WHO) grading system, tumour node metastasis (TNM) stage, Jewett–Whitmore staging system and prostate-specific antigen (PSA) levels [13]. Therefore, more studies of the association of body size with prostate cancer separately by both grade and stage are needed.

The current study is an extended analysis of the association between body size and prostate cancer incidence in the European Prospective Investigation into Cancer and Nutrition (EPIC), with an additional 5 years of follow-up (13.9 compared to 8.5 years in the previous publication) and almost three times the number of incident cases (7024 compared to 2446 cases, including 726 compared to 580 high grade, and 1388 compared to 499 advanced stage cases), and a substantial number of deaths from prostate cancer ($n = 934$) [14]. Herein, we sought to examine the association of height and adiposity at baseline with both prostate cancer risk by tumour characteristics and with prostate cancer death.

Methods

Study cohort

EPIC is a multicentre prospective cohort study designed to investigate the relationships between diet, lifestyle, environmental factors and cancer risk. All participants gave informed consent, and approval of the study was obtained from the Internal Review Board of the International Agency for Research on Cancer (Lyon, France) and from ethics committees at the participating institutions. The full list of all local ethics committees is provided in Additional file 1: Table S1. The methods of recruitment (questionnaires, anthropometric measurements and blood samples) and study design have been previously described [15]. The EPIC cohort consists of 519,978 participants (of whom approximately 150,000 are men) from 23 centres in 10 European countries. Nearly all EPIC participants are white European. In the present study, we describe data for men from 19 centres in 8 of these countries; no data were available for France, Naples (Italy), Norway, and Utrecht (Netherlands) because these sub-cohorts only included women. Men were not eligible for this analysis if they had previously been registered as having cancer at the time of completing the baseline questionnaire (other than non-melanoma skin cancer), if they had missing dates of prostate cancer diagnosis or follow-up, or if they had no anthropometric data. The study cohort for these analyses comprised 141,896 men.

Follow-up for prostate cancer incidence and vital status

Follow-up for incident prostate cancer was provided through record linkage to population cancer registries in Denmark, Italy, the Netherlands, Spain, Sweden and the United Kingdom. In Germany and Greece, follow-up was active and a combination of methods was used, including health insurance records, municipality registries, hospital- or physician-based cancer and pathology registries, and active follow-up of study participants and their next of kin; self-reported incident cancers were verified through medical records. Vital status follow-up was collected by record linkage with regional and/or national mortality registries or by active follow-up (in Germany and Greece). A total of 7024 men developed malignant prostate cancer (code: C61) according to the 10th Revision of the International Statistical Classification of Diseases, Injuries and Causes of Death [16].

Data on TNM stage and histological grade were collected from each centre, where possible. Grade was stratified as low-intermediate (Gleason score of < 8 or grade coded as well, moderately or poorly differentiated; $n = 3749$) or high grade (Gleason score of ≥ 8, or grade coded as undifferentiated; $n = 726$) (Additional file 1: Table S2). Advanced stage cases were tumours that had spread beyond the prostate at diagnosis (T_3–T_4 and/or N_1–N_3 and/or M_1, and/or stage coded in the recruitment centre as metastatic, n = 1388).

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Localised stage cases were those confined within the prostate and with no metastases at diagnosis (TNM staging score of $\leq T_2$ and N_0/N_x and M_0, or stage coded in the recruitment centre as localised, $n = 2634$). Fatal cases were men who died of prostate cancer ($n = 934$).

Assessment of anthropometrics and other predictor variables

The anthropometry protocols in the EPIC study centres have been previously described in detail [17]. Anthropometric data were directly measured by trained study personnel in most of the participants, but it was self-reported in the majority of participants from EPIC-Oxford, although the accuracy of these self-reported data has been validated [18]. Briefly, weight and height were measured with participants wearing no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in metres squared (kg/m^2). Waist circumference was measured either at the narrowest torso circumference or at the midpoint between the lower ribs and iliac crest or a combination of these methods. Hip circumference was measured at the level of the largest lateral extension of the hips or over the buttocks. To compute the waist to hip ratio (WHR), waist circumference was divided by hip circumference. Each participant's anthropometric data were corrected for the clothing worn during measurement in order to reduce heterogeneity due to protocol differences between centres [17]. Weight, height, waist circumference and hip circumference were missing for 640 (0.4%), 391 (0.3%), 13,285 (9.3%) and 15,657 (11.0%) participants, respectively, and these individuals were not included in analyses that include these variables.

Baseline data on lifestyle, health status and socio-demographic characteristics were collected via standardised questionnaires, including diet, medical history, lifetime history of tobacco smoking and alcoholic beverage consumption, physical activity [19], marital status, occupational history and level of education [15]. However, screening data were not available in these analyses.

Statistical analysis

Analyses of the association of anthropometric factors and covariates with prostate cancer risk were conducted by using Cox proportional hazards regression, and hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. The date of last follow-up ranged from January 2011 in Germany to October 2013 in Spain. Age was used as the underlying time variable and data were stratified by centre and age at recruitment (<50, 50–54.9, 55–59.9, 60–64.9, 65–69.9, and ≥ 70 years) in all models. Entry time was defined as age at recruitment, while exit time was age at censoring (i.e. age at last follow-up, first diagnosis of incident cancer, loss to follow-up or death, whichever came first). Exit time for the analysis of prostate cancer death was age when participants died due to the prostate tumour or censoring (other cause of death, lost to follow-up or end of follow-up period for each centre, whichever was first). To check for violation of the proportional hazards assumption we used time-varying covariates and the Schoenfeld residuals, which indicated no evidence of deviation from the proportional hazards assumption. Potential non-linear associations between the anthropometric variables and prostate cancer risk were evaluated using likelihood ratio tests comparing the model with the anthropometric variable entered as an ordered categorical (ordinal) variable to a nested model with the categorical variable treated as continuous, and no evidence of non-linearity was observed. Tests for linear trend were conducted using continuous values for each anthropometric variable. Multivariable models were adjusted for known or suspected risk factors for prostate cancer, including education level (less than university, university graduate, missing), smoking status (never, former, current, missing), marital status (married, not married, missing), diabetes (yes, no, missing), and physical activity (inactive, moderately inactive, moderately active, active, missing) [20].

The following categories for the main exposure variables were used: (1) height (fifths, and per 10 cm increase); (2) BMI (fifths, per 5 kg/m^2 increase, and as predefined WHO categories [21] (<25, 25–29.9, and ≥ 30 kg/m^2)); and (3) waist circumference (fifths, per 10 cm increase, and as predefined WHO categories [22] (<94, 94–101.9, ≥ 102 cm)). The secondary exposure variables were: (1) hip circumference (fifths, and per 10 cm increase) and (2) WHR (fifths, per 0.1 unit increase, and as predefined WHO categories [22] (<0.90, ≥ 0.90)). The fifths were based on fifths of the distribution among non-cases.

Likelihood ratio tests were used to examine the heterogeneity of the associations of the anthropometric variables with risk of prostate cancer categorised according to histological grade (low-intermediate or high grade) and prostate tumour stage (localised or advanced). For this, we fitted stratified Cox models based on competing risks and compared the risk coefficients and standard errors in the subgroups of interest after excluding cases of unknown stage or grade, as appropriate [23].

We also conducted supplementary analyses restricted to high-grade tumours and prostate cancer death to further examine the results from the main analysis. Tests for heterogeneity of trends for the case-defined characteristics (age at diagnosis (<65, ≥ 65 years) and time between blood collection and diagnosis (<5, ≥ 5 years)) were obtained by fitting separate models for each subgroup and assuming independence of the HRs using a competing risk approach. For the non-case-defined

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factors (e.g. age at recruitment (<60, ≥ 60 years)), the test for heterogeneity was assessed by using a likelihood ratio test to compare the Cox models with and without interaction terms for the anthropometric variable and the relevant factor.

Sensitivity analyses was also performed by excluding extreme values (percentiles outside 1–99); additionally adjusting for total intake of energy, alcohol, fruit and vegetables, red meat, processed meat, protein from dairy sources or height; excluding men with missing values for the main covariates; and using the waist circumference-adjusted residuals of BMI and the BMI-adjusted residuals of waist circumference by regressing these variables in a linear regression model and using the residuals (that are statistically independent of waist circumference or BMI, respectively), as the exposures of interest [24].

Statistical analyses were performed with the Stata 14.0 statistical software package 16. All tests of statistical significance were two-sided and *P* values below 0.05 were considered significant.

Results
After an average of 13.9 years of follow-up, a total of 7024 men were diagnosed with prostate cancer among the 141,896 men included in this study. Among the total cases, there were 934 deaths from prostate cancer. The mean age at diagnosis was 67.8 years (range, 41–95 years). The main baseline characteristics of the participants according to categories of BMI (<25, 25–29.9 and ≥ 30 kg/m²) are shown in Table 1 (and by height and waist circumference in Additional file 1: Tables S3 and S4; the distribution of the study participants and of prostate cancer cases by country is shown in Additional file 1: Table S5). Participants with obesity at baseline were more likely to be older, former smokers, moderately inactive and with a lower level of education than were men of normal BMI. Men with obesity were more likely to be missing information on marital status, but of those men who provided information on marital status at recruitment, men with obesity were more likely to be married.

The relationship of height with prostate cancer risk is shown in Table 2. When we compared the highest fifth with the lowest, height was not associated with total prostate cancer risk (HR = 1.06, 95% CI, 0.97–1.15; P_{trend} = 0.3). There was evidence of heterogeneity by tumour grade ($P_{heterogeneity}$ = 0.002), with height being positively associated with high-grade disease (HR = 1.54, 1.18–2.03; P_{trend} = 0.006), but not low-intermediate-grade disease (HR = 0.96, 0.86–1.08; P_{trend} = 0.2). Taller height was also associated with a higher risk for prostate cancer death (HR = 1.43, 1.14–1.80; P_{trend} = 0.001). The risks of high-grade disease and prostate cancer death increased by 21% (HR = 1.21, 1.06–1.38) and 17% (HR = 1.17, 1.04–1.31), respectively, with every 10 cm increment in height.

Table 1 Baseline characteristics of male participants according to body mass index (BMI) categories in the European Prospective Investigation into Cancer and Nutrition (EPIC) study

Characteristic	BMI (kg/m²)		
	<25	25–29.9	≥30
Number of men	50,678	68,736	21,698
Age at baseline,[a] years	50.0 (11.2)	52.5 (9.4)	53.3 (8.9)
Age at diagnosis,[a] years	67.7 (6.9)	68.0 (6.5)	67.7 (6.3)
Smoking status, *N* (%)			
Never smoker	19,156 (37.8)	21,354 (31.1)	5914 (27.3)
Former smoker	15,113 (29.8)	26,916 (39.2)	9162 (42.2)
Current smoker	15,749 (31.1)	19,480 (28.3)	6327 (29.2)
Unknown	660 (1.3)	986 (1.4)	295 (1.4)
Physical activity, *N* (%)			
Inactive	8141 (16.1)	12,998 (18.9)	5309 (24.5)
Moderately inactive	15,452 (30.5)	21,203 (30.8)	6506 (30.0)
Moderately active	12,597 (24.9)	16,636 (24.2)	5046 (23.3)
Active	13,135 (25.9)	16,487 (24.0)	4539 (20.9)
Unknown	1353 (2.7)	1412 (2.1)	298 (1.4)
Diabetes at baseline, *N* (%)			
No	48,380 (95.5)	64,886 (94.4)	19,692 (90.8)
Yes	1088 (2.1)	2424 (3.5)	1542 (7.1)
Unknown	1210 (2.4)	1426 (2.1)	464 (2.1)
Education, *N* (%)			
Below degree level	32,488 (64.1)	50,091 (72.9)	17,485 (80.6)
Degree level	16,644 (32.8)	16,919 (24.6)	3730 (17.2)
Unknown	1546 (3.1)	1726 (2.5)	483 (2.2)
Marital status, *N* (%)			
Married	29,318 (57.9)	38,540 (56.1)	11,029 (50.8)
Not married	9154 (18.1)	7209 (10.5)	2099 (9.7)
Unknown	12,206 (24.1)	22,987 (33.4)	8570 (39.5)
Height,[a] cm	176.2 (7.2)	174.3 (7.2)	172.6 (7.6)
BMI,[a] kg/m²	23.0 (1.6)	27.2 (1.4)	32.6 (2.7)
Weight,[a] kg	71.3 (7.3)	82.7 (7.7)	97.3 (11.4)
Waist circumference,[a] cm	85.8 (6.2)	96.2 (6.2)	109.0 (8.2)
Hip circumference,[a] cm	95.6 (4.6)	101.6 (4.7)	109.7 (6.6)
Waist to hip ratio[a]	0.899 (0.056)	0.948 (0.054)	0.995 (0.057)

[a]Values are means (SD)

Total prostate cancer risk was inversely related to BMI and waist circumference (Table 3); the HRs for highest fifth versus lowest were 0.90 (0.83–0.97, P_{trend} < 0.001) for BMI and 0.92 (0.84–1.00, P_{trend} = 0.01) for waist circumference. However, the association of BMI and waist circumference with prostate cancer risk was found to differ between different prostate cancer tumour characteristics. For BMI and prostate cancer risk, there was evidence of heterogeneity by tumour grade ($P_{heterogeneity}$ = 0.01; HR = 0.89, 0.79–0.99 for low-intermediate-grade and HR = 1.32,

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Table 2 Multivariable-adjusted hazard ratios (95% CI) for prostate cancer in relation to height at recruitment in men from the European Prospective Investigation into Cancer and Nutrition (EPIC) study

	No. of cases	Fifths					P for trend[1]	P for het.[2]	Continuous per 10 cm
		1	2	3	4	5			
		HR	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)			HR (95% CI)
Height, cm									
Median (range)		165.2 (115.0–168.5)	171.0 (168.5–173.0)	175.0 (173.0–176.7)	178.9 (176.7–181.0)	184.2 (181.0–210.0)			
Total prostate cancer	7010	1.00 ref	1.04 (0.96–1.12)	1.02 (0.94–1.10)	1.02 (0.94–1.10)	1.06 (0.97–1.15)	0.3		1.02 (0.98–1.06)
Grade									
Low-intermediate	3740	1.00 ref	0.96 (0.87–1.06)	0.97 (0.88–1.08)	0.91 (0.82–1.01)	0.96 (0.86–1.08)	0.2		0.97 (0.92–1.03)
High	726	1.00 ref	1.30 (1.02–1.66)	1.39 (1.08–1.79)	1.35 (1.04–1.74)	1.54 (1.18–2.03)	0.006	0.002	1.21 (1.06–1.38)
Stage									
Localised	2632	1.00 ref	1.02 (0.91–1.15)	1.01 (0.89–1.14)	0.93 (0.82–1.06)	1.01 (0.88–1.16)	0.7		0.98 (0.92–1.05)
Advanced	1387	1.00 ref	1.04 (0.88–1.24)	1.11 (0.92–1.32)	1.13 (0.95–1.35)	1.09 (0.90–1.32)	0.4	0.2	1.06 (0.96–1.16)
Prostate cancer deaths	932	1.00 ref	1.13 (0.92–1.39)	1.17 (0.94–1.46)	1.13 (0.91–1.41)	1.43 (1.14–1.80)	0.001		1.17 (1.04–1.31)

Cox regression analysis. All models are stratified by centre and age at recruitment and adjusted for education level (less than university, university graduate, missing), smoking status (never, former, current, missing), marital status (married, not married, missing), diabetes (yes, no, missing), and physical activity (inactive, moderately inactive, moderately active, active, missing)

[1] P values for trend are obtained by entering the continuous height in the model

[2] P value from test for heterogeneity for the associations of height with risk of prostate cancer categorised according to prostate tumour grade (low-intermediate or high) and stage (localised or advanced)

Low-intermediate grade (Gleason score of < 8, or grade coded as well, moderately, or poorly differentiated). High grade (Gleason score of ≥ 8, or grade coded as undifferentiated). Localised stage (TNM staging score of ≤ T₂ and N0/Nx and M0, or stage coded in the recruitment centre as localised). Advanced stage (T₃–T₄ and/or N₁–N₃ and/or M1, and/or stage coded in the recruitment centre as metastatic)

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Table 3 Multivariable-adjusted hazard ratios (95% CI) for prostate cancer in relation to body mass index (BMI) and waist circumference at recruitment in men from the European Prospective Investigation into Cancer and Nutrition (EPIC) study

	No. of cases	Fifths					P for trend[1]	P for het[2]	
		1	2	3	4	5			
		HR	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)			
BMI, kg/m²									Continuous per 5 kg/m²
Median (range)		22.2 (12.7–23.5)	24.5 (23.5–25.3)	26.1 (25.3–27.0)	28.0 (27.0–29.2)	31.1 (29.2–68.4)			
Total prostate cancer	6991	1.00 ref	0.99 (0.92–1.07)	1.04 (0.96–1.12)	0.94 (0.87–1.01)	0.90 (0.83–0.97)	<0.001		0.94 (0.90–0.98)
Grade									
Low-intermediate	3727	1.00 ref	0.98 (0.88–1.09)	1.08 (0.97–1.20)	0.90 (0.80–1.00)	0.89 (0.79–0.99)	0.001		0.92 (0.87–0.98)
High	720	1.00 ref	1.38 (1.07–1.77)	1.30 (1.01–1.68)	1.32 (1.02–1.71)	1.32 (1.01–1.72)	0.07	0.01	1.10 (0.97–1.25)
Stage									
Localised	2622	1.00 ref	1.03 (0.91–1.17)	1.00 (0.88–1.14)	0.91 (0.80–1.03)	0.86 (0.75–0.99)	0.001		0.90 (0.84–0.97)
Advanced	1384	1.00 ref	1.04 (0.87–1.24)	1.24 (1.05–1.48)	1.08 (0.90–1.29)	1.11 (0.92–1.33)	0.3	0.01	1.05 (0.96–1.15)
Prostate cancer deaths	931	1.00 ref	1.15 (0.93–1.42)	1.20 (0.97–1.48)	1.05 (0.84–1.31)	1.35 (1.09–1.68)	0.01		1.14 (1.02–1.27)
Waist, cm									Continuous per 10 cm
Median (range)		82.5 (51.0–86.0)	89.0 (86.0–91.9)	94.0 (91.9–96.5)	99.5 (96.5–103.0)	108.0 (103.0–180.0)			
Total prostate cancer	6352	1.00 ref	1.01 (0.93–1.09)	1.00 (0.93–1.07)	0.99 (0.91–1.07)	0.92 (0.84–1.00)	0.01		0.97 (0.94–1.00)
Grade									
Low-intermediate	3251	1.00 ref	0.97 (0.87–1.09)	0.97 (0.86–1.09)	0.95 (0.85–1.06)	0.87 (0.77–0.99)	0.003		0.95 (0.91–0.99)
High	641	1.00 ref	1.36 (1.02–1.81)	1.26 (0.94–1.67)	1.58 (1.20–2.08)	1.43 (1.07–1.92)	0.001	0.002	1.13 (1.03–1.25)
Stage									
Localised	2075	1.00 ref	0.96 (0.82–1.11)	0.96 (0.83–1.11)	0.93 (0.80–1.08)	0.89 (0.76–1.03)	0.03		0.96 (0.91–1.01)
Advanced	1291	1.00 ref	1.20 (1.00–1.46)	1.17 (0.97–1.41)	1.30 (1.08–1.56)	1.08 (0.89–1.32)	0.2	0.1	1.03 (0.96–1.10)
Prostate cancer deaths	877	1.00 ref	1.21 (0.96–1.53)	1.03 (0.81–1.31)	1.28 (1.02–1.61)	1.55 (1.23–1.96)	<0.001		1.18 (1.08–1.28)

Cox regression analysis. All models are stratified by centre and age at recruitment and adjusted for education level (less than university, university graduate, missing), marital status (married, not married, missing), diabetes (yes, no, missing), and physical activity (inactive, moderately inactive, moderately active, active, missing) smoking status (never, former, current, missing)
[1] *P* values for trend are obtained by entering the continuous anthropometric variable in the model
[2] *P* value from test for heterogeneity for the associations of the anthropometric variable with risk of prostate cancer categorised according to prostate tumour grade (low-intermediate or high) and stage (localised or advanced)
Low-intermediate grade (Gleason score of < 8, or grade coded as well, moderately, or poorly differentiated). High grade (Gleason score of ≥ 8, or grade coded as undifferentiated). Localised stage (TNM staging score of ≤ T₂ and N0/Nx and M0, or stage coded in the recruitment centre as localised). Advanced stage (T₃–T₄ and/or N₁–N₃ and/or M1, and/or stage coded in the recruitment centre as metastatic)

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1.01–1.72 for high-grade cancer) and stage ($P_{\text{heterogeneity}}$ = 0.01; HR = 0.86, 0.75–0.99 for localised stage and HR = 1.11, 0.92–1.33 for advanced stage). Similarly, there was significant heterogeneity in the association with waist circumference by tumour grade ($P_{\text{heterogeneity}}$ = 0.002; HR = 0.87, 0.77–0.99 for low-intermediate-grade and HR = 1.43, 1.07–1.92 for high-grade cancer), but not by tumour stage ($P_{\text{heterogeneity}}$ = 0.1). There were statistically significant positive associations of prostate cancer death with BMI (HR = 1.35, 1.09–1.68) and waist circumference (HR = 1.55, 1.23–1.96).

The associations of hip circumference and WHR with prostate cancer risk are shown in Additional file 1: Table S6. Total prostate cancer was inversely associated with hip circumference (HR for highest versus lowest fifth 0.86, 0.79–0.94). There was significant heterogeneity for hip circumference by tumour grade ($P_{\text{heterogeneity}}$ < 0.001; HR = 0.84, 0.75–0.95 for low-intermediate-grade and HR = 1.37, 1.04–1.80 for high-grade cancer). WHR was not associated with total prostate cancer incidence. However, there was evidence of heterogeneity by cancer grade ($P_{\text{heterogeneity}}$ = 0.004) and stage ($P_{\text{heterogeneity}}$ = 0.02); WHR was positively associated with high-grade (HR = 1.46, 1.09–1.94, P_{trend} = 0.004) and advanced stage (HR = 1.29, 1.05–1.58, P_{trend} = 0.01), but not with low-intermediate-grade and localised prostate cancer. Hip circumference was significantly associated with risk of death from prostate cancer (HR for highest versus lowest fifth 1.43, 1.14–1.79), but no association between WHR and prostate cancer death was observed.

When BMI, waist circumference and WHR were categorised according to the WHO cut-off points, the results were broadly similar to those for these variables categorised in fifths (Additional file 1: Table S7).

There was no evidence of heterogeneity for the associations of height, BMI and waist circumference with high-grade prostate cancer and prostate cancer death by age at recruitment (<60, ≥ 60 years), age at diagnosis (<65, ≥ 65 years), or time between recruitment and diagnosis (<5, ≥ 5 years) (Additional file 1: Tables S8 (height), S9 (BMI) and S10 (waist circumference)).

The significant positive association of height, BMI and waist circumference with high-grade prostate cancer and prostate cancer death remained largely unchanged in the sensitivity analysis. After excluding men with missing data for covariates, we observed that the association of waist circumference with both high-grade prostate cancer and prostate cancer death was slightly larger, although the associations of height and BMI with risk were somewhat attenuated and were no longer statistically significant. When we used waist circumference-adjusted residuals of BMI as the exposure, the positive association between BMI and prostate cancer death was no longer statistically significant and the direction was reversed (HR = 0.80, 0.51–1.25). When we used BMI-adjusted residuals of waist circumference as the exposure the association between waist circumference and prostate cancer death was essentially unchanged.

Discussion

In this prospective analysis, men who were taller and with greater adiposity had an elevated risk of high-grade prostate cancer and death from prostate cancer. The associations were strongest for height and waist circumference.

Previous studies have found a positive association between height and risk of prostate cancer [3, 5, 12, 25–30]. In our study, this positive association was only significant for high-grade prostate cancer and death from prostate cancer. While several prospective studies have found a positive association between height and death from prostate cancer [3, 27, 28], to our knowledge, no previous study has found a positive association between height and high-grade prostate cancer risk [3, 29, 30]. However, this might be due to the fact that not many studies have differentiated between prostate cancer stage and grade of the disease [12]. The mechanisms underlying this association of height with aggressive disease are not fully understood. Height is partly determined by genetic factors and it might also be a marker of cumulative early-life growth factor exposures, such as high IGF-I or childhood nutrition, which may increase the risk of prostate cancer [2]. Taller men have more cells (including stem cells) and larger prostate volumes [31]. However, men with smaller prostates have been found to have more high-grade/advanced disease and higher progression rates [32].

Results from previous prospective studies have suggested that the association between obesity and prostate cancer may vary significantly across tumour characteristics [3, 6–9], with a positive association between adiposity and risk of aggressive (advanced stage and high grade combined) prostate cancer [3, 6–9]. The association between genetically determined adiposity and prostate cancer risk has also recently been examined in a large Mendelian randomisation study [33]. No association was observed between genetic score for adult BMI and WHR for total and aggressive prostate cancer (defined as a Gleason score of ≥ 8, a disease stage of 'distant', a PSA level of > 100 ng/mL or death from prostate cancer); however, associations were not examined separately by tumour stage and grade [33]. In our analysis, adiposity tended to be positively associated with risk for high-grade tumours and prostate cancer death, and inversely related to non-aggressive prostate cancer tumours and total prostate cancer, which is in accordance with previous reports [9, 11, 34]. The association of obesity with death might be for a specific tumour subtype such as tumours with the TMPRSS2:ERG gene fusion [35].

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BMI adjusted for waist circumference probably reflects lean body mass rather than adiposity. The positive association between waist circumference and prostate cancer death was the only one maintained in all of the multiple sensitivity analyses. Although waist circumference and BMI are highly correlated, waist circumference has been proposed as a better marker of adiposity for men [36].

In our analysis, adiposity markers tended to be positively associated with aggressive tumours and prostate cancer mortality, and inversely related to non-aggressive prostate cancer tumours and total prostate cancer. These different associations by tumour characteristics may be partly due to differences in prostate cancer detection in men with obesity. Such men may be less likely to be diagnosed with prostate cancer overall, and in particular with early prostate cancer, because they have lower PSA concentrations (perhaps due to an increased blood volume since the total amount of PSA in blood does not differ by body mass), are less likely to undergo a biopsy, and are also likely to have larger prostates, making cancer detection more difficult [37]. It may be also more difficult to perform a thorough digital rectal examination on men with obesity. A reduced likelihood of early detection and treatment might in turn lead to an elevated incidence of aggressive disease and high prostate cancer mortality in men with obesity [38]. However, several possible biological mechanisms that may underlie the association between obesity and prostate cancer death have been proposed, including mechanisms that involve insulin and the IGF-I axis, sex hormones, and inflammatory and oxidative stress pathways. Obesity is associated with disturbances in the IGF-I axis; an inverted U-shaped association between BMI and IGF-I has been observed, while BMI and concentrations of IGFBP-1 and -2 have been shown to be inversely associated [39]. High circulating IGF-I levels are associated with an increased prostate cancer incidence in this cohort [40] and in an individual participant meta-analysis of prospective studies [2]. Participants with obesity normally suffer from hyperinsulinemia, which has been linked to prostate cancer risk [41] and prostate cancer mortality [42]. Obesity is also related to a decrease in free testosterone and changes in other sex hormone concentrations [38]. Moreover, excess adiposity may contribute to the activation of proinflammatory signalling pathways [43] and higher oxidative stress [44], both of which have been suggested to be linked to higher prostate cancer risk [45, 46].

This study has several strengths and also some limitations. The strengths include its prospective design, detailed information on potential confounders, long follow-up, the large sample size and number of incident cases, and the availability of data on prostate cancer tumour characteristics and mortality. Analyses by time to diagnosis showed

no evidence that the observed associations were due to reverse causality. Although measurements of fat mass were not available in this study, previous investigations have shown that both BMI and waist circumference are strongly correlated with total fat mass [47]. Participants in this cohort might be considered to be late middle-aged adults, since their mean age at recruitment was 52 years. In this age group, and especially in older adults, the use of BMI as a measure of overweight and obesity might be less sensitive because ageing is associated with a decrease in muscle mass and height [48]. It might therefore be argued that the use of BMI in our cohort may lead to an underestimate in the prevalence of obesity; however, we also use waist circumference, which has been found to be a better predictor of total body fat, and especially of abdominal adiposity in men, than BMI, because waist circumference is less influenced by muscle mass [48]. The lack of screening data is a limitation of this analysis. Information on tumour characteristics was only available for a subset of cases (24.8% of prostate cancer cases did not have any data on tumour characteristics) and men with obesity were less likely to have missing data on tumour stage and grade than were men who were not overweight. Data on early-life factors, including anthropometry, which may influence prostate cancer occurrence [26, 49], were not available in the current study.

Conclusion

In summary, the findings from this large European prospective study provide evidence that men with greater height and adiposity (high BMI and waist circumference) have an elevated risk of high-grade prostate cancer and prostate cancer death. The data presented illustrate the complex association of adiposity and prostate cancer, which varies by disease aggressiveness.

Additional file

Additional file 1: Table S1. List of all of the local ethics committees for the European Prospective Investigation into Cancer and Nutrition (EPIC) study. **Table S2.** Distribution of cases by tumour grade in men from the EPIC study. **Table S3.** Baseline characteristics of participants according to fifths of height at recruitment in men from the EPIC study. **Table S4.** Baseline characteristics of participants according to fifths of waist circumference at recruitment in men from the EPIC study. **Table S5.** Distribution of study participants and prostate cancer cases by country. **Table S6.** Multivariable-adjusted hazard ratios (95% CI) for prostate cancer in relation to hip circumference and waist to hip ratio (WHR) at recruitment in men from the EPIC study. **Table S7.** Multivariable-adjusted hazard ratios (95% CI) for prostate cancer in relation to BMI, waist circumference and WHR using the WHO cut-off points at recruitment in men from the EPIC study. **Table S8.** Stratified and sensitivity analyses. Multivariable-adjusted hazard ratios (95% CI) for high-grade prostate cancer and death from prostate cancer in relation to height (per 10 cm unit increase) at recruitment in men from the EPIC study. **Table S9.** Stratified and sensitivity analyses. Multivariable-adjusted hazard ratios (95% CI) for high-grade prostate cancer and death from prostate cancer in relation to BMI (per 5 kg/m^2 unit increase) at recruitment in men from the EPIC study.

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Table S10. Stratified and sensitivity analyses. Multivariable-adjusted hazard ratios (95% CI) for high-grade prostate cancer and death from prostate cancer in relation to waist circumference (per 10 cm unit increase) at recruitment in men from the EPIC study. (DOCX 63 kb)

Abbreviations
BMI: body mass index; CIs: confidence intervals; EPIC: European Prospective Investigation into Cancer and Nutrition; HRs: hazard ratios; IGF-I: insulin-like growth factor I; PSA: prostate-specific antigen; TNM: tumour node metastasis; WHO: World Health Organization; WHR: waist to hip ratio

Availability of data and materials
EPIC data are available for investigators who seek to answer important questions on health and disease in the context of research projects that are consistent with the legal and ethical standard practices of IARC/WHO and the EPIC Centres. The primary responsibility for accessing the data belongs to the EPIC centres that provided them. For information on how to submit an application for gaining access to EPIC data and/or biospecimens, please follow the instructions at http://epic.iarc.fr/access/index.php.

Authors' contributions
The authors' responsibilities were as follows. AP-C, TJK and RCT conceived and designed the research. AP-C analysed the data. AP-C, PNA, TJK and RCT were responsible for drafting the manuscript. TP, KKT, AT, AO KO, RK, TK, HB, AS, AT, PL, MK, VK, DP, CS, RT, HBB-d-M, AA, NL, EM-P, AB, MDC, JRQ, PS, CH, NW, KTK, JAS, MG, HF, DA and HW provided the original data, information on the respective populations, and advice on the study design, analysis and interpretation of the results. ER was the overall coordinator of the EPIC project, which was conceptualised, designed and implemented in collaboration with the principal investigators in the collaborating centres. All of the authors read and approved the final manuscript. None of the authors had financial or non-financial interests relevant to the submitted manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
This study complies with the Declaration of Helsinki. Ethical review boards of IARC and all local institutions where participants had been recruited gave approval for the study, and all participants gave written informed consent for data collection and storage, as well as individual follow-up. The full list of all the local ethics committees that granted approval for the EPIC study can be found in Additional file 1: Table S1.

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