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Body size across the life course and prostate cancer in the Health Professionals Follow-up Study

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Abstract

Current evidence of an association between body size and prostate cancer is conflicting, possibly due to differential effects of body size across the lifespan and the heterogeneity of the disease. We therefore examined childhood and adult body size in relation to total incident prostate cancer and prognostic subtypes in a prospective cohort of 47,491 US men in the Health Professionals Follow-up Study. We assessed adult height, body mass index (BMI) in early and middle-to-late adulthood, adult waist circumference, and body shape at age 10. With follow-up from 1986 to 2010, we estimated the relative risk (RR) of prostate cancer using Cox proportional hazards models. We identified 6183 incident cases. Tallness was associated with increased risk of advanced-stage tumors, particularly fatal disease (RR=1.66, 95% CI 1.23–2.23, highest versus lowest quintile, P_{trend}<0.001). High BMI at age 21 was inversely associated with total prostate cancer (RR=0.89, 95% CI 0.80–0.98, BMI ≥26 versus 20–21.9, P_{trend}=0.01) and with fatal and advanced disease. The association for late adult BMI differed by age ($P_{interaction}$<0.001); high BMI was inversely associated with total prostate cancer (RR=0.64, 95% CI 0.51–0.78, BMI ≥30 versus 21–22.9, P_{trend}<0.001) and with non-advanced and less aggressive tumors among men ≤65 years, whereas no association was seen among men >65 years. Adult waist circumference was weakly inversely associated with less aggressive disease. Childhood obesity was unclearly related to risk. Our study confirms tall men to be at increased risk of fatal and advanced prostate cancer. The influence of adiposity varies by prognostic disease subtype and by age.

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Conflict of interest

The authors declare no conflicts of interest.

Keywords

prostatic neoplasms; height; body mass index; childhood body size; waist circumference; epidemiology

Introduction

Body size is related to various hormonal and metabolic pathways and may therefore influence the risk of developing prostate cancer, a largely hormone-dependent cancer. However, current evidence of an association is conflicting. Prostate cancer is a heterogeneous disease and the etiology seems to differ between prognostic tumor subtypes and between different groups of men (e.g. younger versus older). The timing of body size throughout life may have unique influences on disease pathogenesis. In light of the obesity epidemic in the Western world, it is crucial to clarify the etiological role of body size in prostate cancer development for future cancer preventive strategies.

Tall adult height has been associated with increased risk of prostate cancer [1–5]. High body mass index (BMI) in middle-to-late adulthood has been suggested to increase the risk of advanced and fatal prostate cancer, but reduce the risk of localized disease [3,6,7]. Body size early in life is potentially independently important since early changes in prostate tissue have been seen already in men in their twenties [8]. For body size in early adulthood (≤30 years) the findings are inconsistent [2,9–12]. Obesity in childhood has been inversely associated with risk of total, advanced, or aggressive prostate cancer [11,13,14], whereas other studies have shown no association [15,16].

The present study is an updated investigation of childhood and adult body size and prostate cancer incidence and progression in the Health Professionals Follow-up Study [14]. This is one of the largest observational studies on men, with over 6000 prostate cancer cases and prospectively updated information on lifestyle and health since 1986 as well as early-life anthropometric data. The prior analysis showed strong positive associations between adult height and advanced/metastatic prostate cancer, and inverse associations between obesity at age 5, 10, and 20 and advanced/metastatic disease. In the current study with 16 additional years of follow-up we examined adult height, BMI at age 21, cumulative average BMI since baseline, adult waist circumference, and body shape at age 10 in relation to total incident prostate cancer and different tumor subtypes. We further investigated the effect estimates of all anthropometric measures stratified by age at diagnosis and family history of the disease, as these factors have previously been shown to modify the associations between BMI, waist circumference and prostate cancer [10,17].

Methods

Study population

The Health Professionals Follow-up Study is a prospective cohort of 51,529 US male health professionals [18]. The participants, aged 40–75 years at enrolment in 1986, completed a baseline questionnaire on medical and lifestyle factors and have been followed through self-administered questionnaires every two years for updated information, with an average

response rate >94%. The study and use of the data are continually approved by the Institutional Review Board of the Harvard School of Public Health.

We excluded erroneous reports (n=39) and men who left ≥70 items blank in the 1986 dietary questionnaire or who reported unreasonably high (>17,600 kJ) or low (<3350 kJ) energy intakes (n=1596). We further excluded men with cancer, except non-melanoma skin cancer, at baseline (n=2009) and men with missing values for height (n=32) or weight in both 1986 and 1988 (n=362). Among the 47,491 men who remained for analyses after exclusions, the number of men with complete data on BMI at age 21 was 45,695, on waist circumference 31,069, and on childhood body shape 34,983.

Anthropometric measures

Height, current weight, and weight at age 21 were self-reported on the 1986 baseline questionnaire. Current weight has been updated every two years. We calculated BMI (kg/m^2) at age 21, at baseline, and the cumulative average at each follow-up. Cumulative average BMI was the average of BMI values for each questionnaire up to that follow-up cycle; for example, the average of 1986, 1988, and 1990 BMI was used as the cumulative average BMI for the 1990 cycle. If data on weight was missing at one follow-up, then data from the previous questionnaire cycle was used. Information on waist circumference was obtained through an additional questionnaire in 1987 where participants were asked to measure their waist with a provided tape measure and detailed instructions, and this measurement was repeated in 1996. Self-reported weight and waist circumference have been strongly correlated with objectively measured values in a sample of the cohort (r=0.97 and 0.95, respectively) [19].

Body shape at different ages was assessed in the 1988 questionnaire through a pictogram with drawings of silhouettes of nine different sizes, ranging from very thin to obese (Fig. 1) [20]. Participants were asked to select the silhouette that best represented their body shape at age 5, 10, 20, 30, 40, and current age, respectively. We focused on body shape at age 10 because the previous investigation showed this variable to be most strongly associated with prostate cancer [14]. A validation study in elderly individuals showed high correlation (r=0.66) between recalled body shape at age 10 assessed by the pictogram and weight measured in childhood [21].

Outcome measures

Prostate cancer diagnoses were identified through self-reports and confirmed by medical records and pathology reports. Next-of-kin was contacted if the participant had died. Greater than 90% of the prostate cancer cases were confirmed by medical records; the remaining were included in total prostate cancer analyses since the accuracy among those with available records is >98%. Information on tumor pathology and prostate-specific antigen (PSA) values were obtained through medical records and pathology reports at diagnosis. Starting in 2000, men with a prostate cancer diagnosis were followed with biennial questionnaires on disease progression and metastases. Death reports were retrieved from family members or the National Death Index, ascertaining approximately 98% of all deaths

in the cohort. Prostate cancer was determined as cause of death based on all available information from medical records, registry, and death certificates.

We investigated incidence of total prostate cancer as well as risk stratified by grade and stage of disease. Lethal cases were those who died of prostate cancer or had distant metastases at diagnosis or during follow-up. We also analyzed fatal disease (i.e., death from prostate cancer) separately, because body size could plausibly affect the risk of dying from prostate cancer independently of affecting the risk of metastases. Advanced cases included tumors that had spread outside the prostate at diagnosis (stage T3b/T4, N1, or M1) or lethal tumors. Non-advanced tumors included those confined within the prostate and with no metastases at diagnosis (stage T1/T2, N0, and M0), and did not cause any metastases or prostate cancer-specific death during follow-up. We did not include T1a tumors (n=254) in our case definition as these are relatively benign and prone to detection bias; these patients were censored at date of diagnosis. We defined high-grade (aggressive) prostate cancer as Gleason score 8–10 and low-grade (non-aggressive) tumors as Gleason score 2–6, and examined Gleason score-7 cases separately.

Statistical analysis

Participants were followed until January 31, 2010. Person-time was calculated from the month of return of the 1986 questionnaire until the month of prostate cancer diagnosis, month of death from any cause, or end of follow-up. For analyses of childhood body shape, follow-up time started at return of the 1988 questionnaire when the data were collected. For cumulative average BMI and waist circumference, we excluded the first two years of follow-up to avoid the risk of reverse causality due to disease-related weight loss.

All categorizations of variables were done a priori (see tables); different categorizations were used for BMI at age 21 and later adult BMI because the distribution of BMI was different for early and later adulthood. To test for linear trends across categories we modeled the exposures as continuous variables, using the median value in each category of height, BMI, and waist circumference. We also modeled the continuous exposures as a 2-inch increment in height, a 5 kg/m^2 increment in BMI, and a 1-inch increment in waist circumference, respectively. The correlation between exposures was estimated by Spearman correlation coefficients.

We used Cox proportional hazards regression with age as the time scale to estimate the relative risk (RR) of prostate cancer as hazard ratios with 95 % confidence intervals (CI). All models were stratified by calendar time. Multivariable models were additionally adjusted for a priori selected covariates gleaned from the baseline or follow-up questionnaires: ethnicity, vigorous activity, energy intake, smoking, diabetes, family history of prostate cancer (father or brother), PSA test (assessed from 1994 onwards), and PSA testing intensity (PSA test in < or ≥ 50% of periods); both PSA variables were lagged one period to avoid counting diagnostic tests as screening. We also considered multivitamin use and intake of alcohol, calcium, coffee, red/processed meat, and tomato sauce as potential confounders, but they were not included in the final models as they did not influence the results. The questions on diet and physical activity have been validated in sub-samples of the cohort [22,23], and self-reported diabetes has been validated in a population of female health professionals [24].

Additionally, we mutually adjusted for the anthropometric measures in some models. Information on weight, activity, diet, smoking, diabetes, and PSA testing were used as time-varying variables and were updated at each questionnaire cycle. Information on family history of prostate cancer was updated several times throughout follow-up.

We tested the proportional hazards assumption (proportionality across both time and age) using likelihood ratio tests. We further investigated the effects of all anthropometric measures stratified by age and family history of prostate cancer. To explore whether the results were heavily affected by PSA screening, we performed additional analyses restricted to the cohort of highly screened men having had a PSA test in 1994 or 1996, with follow-up from 1996 to 2010, and with continued adjustment for PSA testing over time in the models.

All P values are two-sided, with $P<0.05$ considered as statistically significant. We used SAS version 9.3 (SAS Institute Inc., Cary, NC) for all analyses.

Results

Total follow-up time was 24 years, with an accumulated 938,614 person-years; with baseline in 1988 there were 22 years of follow-up and 852,890 accumulated person-years. We identified 6183 prostate cancer cases, of whom 618 were fatal, 785 lethal, 1016 advanced, 3990 non-advanced, 707 high-grade (Gleason 8–10), 1776 Gleason 7, and 2476 low-grade (Gleason 2–6) cases.

Age-standardized characteristics did not vary appreciably by anthropometric variables, except that vigorous physical activity was much lower in men with high cumulative average BMI or high waist circumference (table 1). Height was uncorrelated with the other anthropometric measures (r_s in the range −0.03 to −0.001) with the exception of waist circumference (r_s=0.22). The two BMI measures (at age 21 and adult cumulative average) were moderately correlated (r_s=0.47). Waist circumference correlated weakly with height (r_s=0.22), young adult BMI (r_s=0.27) and strongly with cumulative average BMI (r_s=0.70). Childhood body shape was weakly correlated with adult body size (r_s=0.38, 0.18, and 0.09, respectively for BMI at age 21, cumulative average BMI, and waist circumference).

The results were overall similar between age- and multivariable-adjusted models, therefore only the latter are shown in tables.

Tallness was positively related to fatal, lethal, advanced, and Gleason 7 prostate cancer (Table 2). The association was strongest for fatal disease; the risk of dying from prostate cancer increased by 15% (95% CI 1.08–1.22) with every 2 inch increment in height, and by 66% (95% CI 1.23–2.23) comparing the highest quintile to the lowest ($P_{trend}<0.001$). We also observed an inverse association with low-grade disease, whereas there was no association for high-grade disease. The associations were not affected by adjusting for childhood or adult body size (data not shown).

Higher BMI at age 21 was associated with significantly lower risk of lethal, advanced, and Gleason-7 prostate cancer, with multivariable-adjusted RRs in the range 0.69–0.77 comparing BMI ≥26 to BMI 20–21.9. However, a significant trend was seen across BMI

categories only for advanced and Gleason-7 (Table 3). We observed weak inverse associations for total, non-advanced, and low-grade prostate cancer.

The association between cumulative average BMI since baseline and prostate cancer risk was found to be non-proportional over age (P<0.001 for total prostate cancer); therefore we report the results stratified by age at diagnosis (Table 4). Among men 65 years or younger, BMI was inversely associated with total, non-advanced, Gleason-7, and low-grade prostate cancer. We observed no significant associations in men >65 years.

The associations between age 21 and adult BMI and prostate cancer were somewhat attenuated when additionally adjusting for childhood body shape, or mutual adjustment for BMI in early or late adulthood, respectively (Supplemental Tables 1 and 2), but not for height or waist circumference (data not shown).

Waist circumference was not associated with risk of total prostate cancer (multivariable-adjusted RR for each quintile versus lowest quintile: Q2: 1.09, 95% CI 1.00–1.20, Q3: 1.01, 95% CI 0.91–1.10, Q4: 1.00, 95% CI 0.91–1.10, Q5: 0.97, 95% CI 0.88–1.06, P_{trend}=0.10; continuous per 1-inch increase: 0.99, 95% CI 0.99–1.00). Higher waist circumference was associated with lower risk of non-advanced (multivariable-adjusted RR for top versus bottom quintile: 0.93, 95% CI 0.82–1.04, P_{trend}=0.03), Gleason-7 (multivariable-adjusted RR 0.84, 95% CI 0.70–1.00, P_{trend}=0.02) and low-grade prostate cancer (multivariable-adjusted RR 0.88, 95% CI 0.75–1.02, P_{trend}=0.01). The observed associations were weakened when adjusting for either childhood body shape or adult BMI. Waist circumference was not associated with other prostate cancer subtypes (data not shown).

Investigating body shape at age 10, we found inverse associations between the middle-size category (silhouette 5) and with risk of total, non-advanced, and low-grade prostate cancer (Table 5). The inverse associations for the most overweight/obese category (silhouettes 6–9) were not statistically significant. We found men in the thinnest category (silhouette 1) to have had a weakly increased risk of total, non-advanced, and Gleason-7 disease compared to the reference group (silhouette 2). Results were similar when stratified by age ≤65 years and >65 years (data not shown).

Beside the interaction between cumulative average BMI and age, we observed no significant interactions between any of the anthropometric variables and age or family history of prostate cancer ($P_{interaction}$ >0.05). However, in stratified analyses the positive associations between tall height and fatal, lethal and advanced disease were more pronounced in men ≤65 years and in men with no family history of prostate cancer, compared to men >65 years or men with an affected father or brother. Furthermore, the observed inverse associations between BMI at age 21 and total, non-advanced, Gleason-7 and low-grade prostate cancer appeared stronger in men ≤65 years compared to older men.

Additional analyses showed overall similar results in the cohort of highly screened men compared to the full cohort (data not shown).

Discussion

In this large prospective cohort study with over 20 years of follow-up, we found taller height to be positively associated with fatal and advanced-stage prostate cancer, in line with prior findings [1,14]. We also confirmed the previously reported inverse association between high BMI at age 21 and advanced and lethal prostate cancer [10,14]. In addition, higher cumulative average BMI was associated with reduced risk of total, non-advanced, and less aggressive disease in men ≤65 years at diagnosis. Waist circumference was weakly inversely associated with less aggressive disease. We observed no clear association between childhood body size and prostate cancer.

Strengths of our study include the prospective design with repeated measures of weight and other lifestyle factors and data on early-life body size. The large study sample with extensive information on tumor stage and grade and long follow-up on progression and mortality enabled detailed analyses of prognostic disease subtypes.

The self-reported measures of body size are a potential limitation. However, self-reported and measured height, weight and waist circumference have been highly correlated in men (r~0.95) [19,25], and recalled weight in early adulthood has been highly correlated with measured weight [21]. The pictogram assessing body shape in different ages has been shown useful to identify thin (silhouettes 1–4) and obese (silhouettes 6–9) individuals [25], and has also shown good correlation with weight measured in childhood [21]. Nevertheless, we cannot rule out potential bias caused by exposure misclassification, although it is most likely non-differential due to the prospective study design.

Our findings on height are in line with other studies. A meta-analysis including thirteen cohort studies yielded a pooled RR for advanced/aggressive/fatal prostate cancer of 1.12 (95% CI 1.05–1.19) for every 10 cm (~3.9 in) increment in height [5]. Another meta-analysis based on 31 cohort studies yielded a pooled estimate for total prostate cancer of 1.09 (95% CI 1.06–1.12) [5]. It is not clear why a positive association was observed between height and grade 7 cancer, but not high-grade cancer; it is possible this was due to lower numbers of high-grade cases.

Our analysis of BMI at age 21 showed a 20–30 % reduced risk of fatal, lethal and advanced disease and a weak risk reduction for total prostate cancer comparing the highest to the lowest BMI category. Other studies show inconsistent evidence of an association between obesity in early adulthood (18–30 years) and prostate cancer. A review of studies on total prostate cancer suggest no or a weak positive relationship [26]. Two studies reported inverse associations with advanced [11] or fatal [9] disease, similar to our findings, whereas others show null associations [2,9,12,27,28]. Findings for non-advanced or non-aggressive prostate cancer are mixed [2,9,12,28].

BMI in middle-to-late adulthood has been contrarily related to prostate cancer across disease subtypes. Meta-analyses have shown modest positive associations with total prostate cancer [3,29], although many individual studies report null findings. This is in contrast to the inverse association observed in the current study. A probable explanation is the stronger inverse association with non-advanced/less aggressive disease, similar to what several other

prospective studies have reported [2,9,17,28,30,31]. A recent meta-analysis based on 12 prospective studies showed an RR of 0.94 (95% CI 0.91–0.97) for localized prostate cancer for every 5 kg/m^2 increase in BMI [7]. For advanced, high-grade, and fatal disease there is evidence of a positive association with obesity [3,6,7,17,31–33]; meta-analyses have yielded RRs in the range 1.09–1.12 for advanced disease for every 5 kg/m^2 increase in BMI [3,7], and RR 1.15 (95% CI 1.06–1.25) for prostate cancer-specific mortality [6]. However, findings are divergent as several cohort studies have found no associations with advanced [2,4,9,12,28,30] or fatal [6] prostate cancer, which is in agreement with the current study.

Waist circumference was not associated with total prostate cancer risk [14]. This is consistent with our previous investigation [14] and two partly overlapping meta-analyses including cohort and case-control studies [3,34]. However, a more recent meta-analysis showed a 56% (P=0.007) increased risk of total prostate cancer for waist circumference >102 cm (40.2 in) [35]. Our findings of an inverse association with less aggressive disease are in agreement with findings in the Prostate Cancer Prevention Trial (RR 0.78, 95% CI 0.66–0.93, highest versus lowest quartile, P_{trend}=0.02) [17]. Positive associations have been suggested for advanced/aggressive prostate cancer in prospective cohort studies [17,30,36].

Previously in our study population, baseline BMI and waist circumference were more strongly associated with total prostate cancer in men <60 years and men with a family history of prostate cancer [10]. In the current study, the inverse associations between BMI in early and late adulthood and non-advanced/less aggressive disease were all stronger in men ≤65 years compared to older men. Furthermore, the association with height appeared to differ between strata of age and family history of prostate cancer, although these results should be interpreted with caution as the formal test for interaction was non-significant. Tumors manifesting in early age or in men with an affected father or brother are mainly hereditary, and the mechanistic pathways of hereditary prostate cancer may differ from those of sporadic tumors [10], although the distinct biologic mechanisms are yet largely unknown.

Although the observed inverse associations between BMI and waist circumference in middle-to-late adulthood and total/non-advanced/low-grade tumors are in agreement with other studies, these results may be influenced by detection bias. Due to lower PSA values and difficulties in performing diagnostic tests [37], obese men are less likely to be diagnosed with prostate cancer, especially at an early stage, than non-obese men. This could weaken or even reverse potentially positive associations between obesity and early-stage tumors. Reverse causation due to disease-related weight loss is not likely to explain the observed findings for adult obesity since it would mainly have affected the estimates for lethal/advanced disease and because we excluded the first two years of follow-up. However, it is unlikely that detection bias or reverse causation would be stronger in the young age group where we observed the strongest associations. Finally, competing risks are a possible explanation for the inverse associations, as men with higher BMI or waist circumference may be at increased risk of death due to other causes, resulting in an apparent protective effect of obesity on prostate cancer diagnosis or death. This would likely play more of a role in the null findings for lethal prostate cancer than for the inverse findings for localized or low-grade disease, because men would need to survive long enough after diagnosis to develop metastatic and eventually fatal prostate cancer. Again, though, competing risks

would likely not explain our stronger findings for younger men, as competing risks play a larger role among older study populations where death rates are higher.

We observed greater attenuation overall when adjusting for BMI at age 21 in analyses of cumulative average BMI or waist circumference than the reverse. This supports our hypothesis that body size in early adulthood is more strongly related to prostate cancer development than body size later in life.

Previous findings of an inverse association between childhood obesity and advanced/metastatic prostate cancer in the same cohort [14] were not confirmed in our updated analysis. Although we found men in the middle-size category in childhood to be at lower risk for total, non-advanced and low-grade disease, no association was seen in the most overweight/obese group. This remained true when results were stratified by age at diagnosis, suggesting that the older age of the cohort does not explain the difference in results from our previous publication. A large Danish cohort study found BMI at age 7–13 to be positively associated with total and localized prostate cancer, but not metastatic disease; however, the associations became non-significant when adjusting for childhood height [15]. Two case-control studies reported lower risk of total or advanced prostate cancer in men being overweight/obese at age 10–13 [11,13]. Other case-control studies did not find any associations with body size at age 8–9 [16] or in adolescence [38–40], though these studies made no distinction between prostate cancer subtypes. In the current study, the observed higher risk of non-advanced and Gleason-7 disease among men the thinnest category may be due to unmeasured confounding factors causing extreme thinness in childhood and should thus be cautiously interpreted.

The results for all exposures were overall stable between age- and multivariable-adjusted models, and additional adjustment for dietary factors produced little differences. However, residual or unmeasured confounding cannot be ruled out in our study. PSA testing is an important covariate that we included. Because men with higher adult BMI were somewhat less likely to have had a PSA test in 1994, the associations with non-advanced/low-grade prostate cancer could potentially be biased towards a more inverse association. However, the results were overall similar in the cohort of highly screened men, so residual confounding by PSA testing is probably not a major explanation.

Plausible biological mechanisms for a potential association between body size and prostate cancer involve hormonal and metabolic pathways that interact in a complex manner. These include the insulin/insulin-like growth factor-I (IGF-I) axis, sex hormones, and inflammation-mediated pathways, although the latter remain largely unclear [41]. High levels of IGF-I [42–44] and insulin [45–47] have been positively linked to prostate cancer risk and mortality, whereas low testosterone levels have been associated with increased risk of aggressive prostate cancer [37,48].

Overweight and obesity in adult men correlate with both higher circulating levels of insulin and free IGF-I, and lower levels of testosterone [41]. However, insulin resistance and long-lasting diabetes, both long-term consequences of obesity, have been inversely associated with prostate cancer, possibly by limiting the negative effects of insulin [41]. It has thus been

suggested that obesity could impose a higher risk of aggressive prostate cancer but a lower risk of non-aggressive disease [34,48], the latter being supported by the current study.

Puberty is associated with a sharp rise in IGF-I levels [49]. Obesity in pre-pubertal age may delay onset of puberty [50], leading to lower exposure of IGF-I at a potentially critical time point in male development, or alternatively lower cumulative lifetime exposure; both could hypothetically lead to a lower risk of developing prostate cancer later in life. Adolescent obesity has been seen to persist in early adulthood [51], thus the observed inverse association between overweight at age 21 and prostate cancer could be the result of lower IGF-I levels.

Attained height is thought to be a marker for early-life factors potentially associated with prostate cancer such as exposure to growth hormones, notably IGF-I, in childhood/adolescence [5]. Supported by the observed positive associations with advanced-stage tumors in our study, the early-life factors predicting height may prime the prostate gland at an early age for later development of a more aggressive tumor. If height is involved in low-grade tumors progressing into high-grade tumors, this could potentially also explain the observed inverse association between height and low-grade disease.

In conclusion, our updated extensive analysis of the Health Professionals Follow-up Study identified tall men to be at increased risk of advanced and fatal prostate cancer. We further showed that the influence of body weight varies by tumor stage and aggressiveness as well as between different periods in life. However, more observational and experimental studies are needed in order to draw conclusions on causality regarding the complex role of body size in prostate cancer development. The timing of exposure as well as disease subtypes are fundamental to consider in future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Novelty & Impact Statement

The relationship between body size and prostate cancer is complex. Body size changes progressively throughout life and consequent affects on prostate cancer risk may be associated with related changes in hormonal and metabolic pathways. This large prospective study examined potential associations between the risk of various prostate cancer subtypes and multiple anthropometric measures at different ages in men. Tallness was confirmed to be associated with an elevated risk of advanced prostate cancer, particularly fatal disease. The extent to which body weight influenced risk varied according to factors such as age and disease subtype.

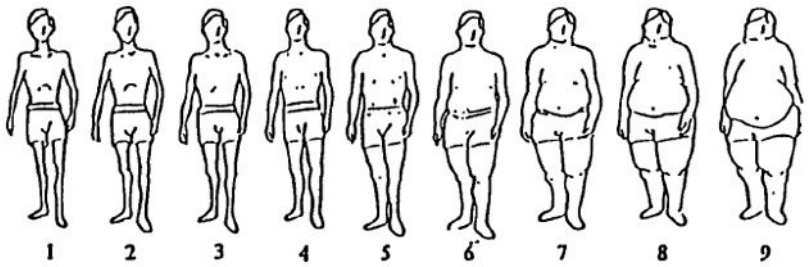

Fig. 1.

Silhouette drawings of body shape in the Health Professionals Follow-up Study, 1988 questionnaire: “Which diagram best depicts your outline at each age (5, 10, 20, 30, 40, current)”. Reproduced from Stunkard *et al.* [20] with permission from Wolters Kluwer/ Lippincott Williams & Wilkins.

Table 1

Age-standardized characteristics of participants in the Health Professionals Follow-up Study at baseline in 1986, by top and reference categories of anthropometric measures

	Height, inches (quintiles)		BMI at age 21, kg/m^2		Cumulative average BMI, kg/m^2		Waist circumference, inches (quintiles)		Body shape at age 10	
	<68 (ref)	≥73	20–21.9 (ref)	≥26	21–22.9 (ref)	≥30 kg/m^2	<34.5 (ref)	>40	Silhouette 2 (ref)	Silhouette 6–9
No. of participants	7423	8150	10987	5404	6849	3933	6231	5984	11175	2994
Age, years	56.9	52.1	55.3	52.9	53.8	54.4	51.8	56.7	55.0	51.1
BMI at age 21, kg/m^2	23.4	23.0	21.1	28.5	21.2	26.9	21.8	24.6	22.4	25.3
BMI in 1986, kg/m^2	25.9	25.5	24.1	29.4	22.1	33.0	22.6	29.0	25.0	26.5
Waist circumference, inches	36.1	38.8	36.4	40.5	34.4	44.1	33.0	43.0	37.1	38.6
Height, inches	66.0	74.0	70.1	69.9	70.1	69.6	69.0	71.0	70.3	70.2
Body shape at age 10[a]										
Silhouette ≥6, %	8	9	3	25	6	17	6	13	-	-
Caucasian, %	90	97	95	97	95	96	94	98	96	97
Had PSA test in 1994, %	38	37	38	36	39	34	38	43	42	40
Family history of prostate cancer, %	11	12	12	12	12	11	13	13	13	12
Diabetes, %	4	3	3	5	3	6	2	4	3	4
Never smoker, %	48	45	47	44	52	42	53	41	49	40
Current smoker, %	9	10	10	11	10	10	9	10	9	11
Multivitamin user, %	42	42	42	40	47	36	47	39	42	43
Vigorous activity, MET-h/wk	12.6	12.8	12.0	12.5	17.5	6.6	19.3	6.8	12.2	14.5
Mean intake										
Total energy, kcal/d	1911	2065	2012	1960	2000	2016	1999	2033	2011	1944
Alcohol, g/d	9.8	12.2	11.5	10.0	10.8	10.2	10.7	11.8	11.5	11.6
Calcium, mg/d	872	923	885	914	917	894	936	899	898	903
Coffee, servings/d	1.8	1.9	1.8	2.0	1.7	2.0	1.6	2.0	1.7	2.3
Red/processed meat, servings/d	0.9	1.0	1.0	1.0	0.9	1.2	0.8	1.1	1.0	0.9
Tomato sauce, servings/d	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1

BMI, body mass index; PSA, prostate-specific antigen; MET, metabolic equivalents.

Values are means or percentages, standardized to the age distribution of the study population (except age).

[a]Based on pictogram in Fig. 1.

Table 2

Relative risk of prostate cancer (PC) in relation to adult height in the Health Professionals Follow-up Study (1986–2010)

		Height (inches)						
		<68	**68–69**	**70**	**71–72**	**≥73**	**P_{trend}**	**Continuous per 2 inches**
Total PC	Cases	1001	1448	1100	1627	1007		
	MV-adj RR[a]	1.00	1.00 (0.91–1.08)	1.04 (0.95–1.13)	1.00 (0.92–1.08)	1.03 (0.94–1.13)	0.69	1.01 (0.99–1.03)
Fatal PC	Cases	96	142	106	169	105		
	MV-adj RR[a]	1.00	1.11 (0.85–1.46)	1.26 (0.94–1.68)	1.42 (1.09–1.86)	1.66 (1.23–2.23)	<0.001	1.15 (1.08–1.22)
Lethal PC[b]	Cases	132	186	135	214	118		
	MV-adj RR[a]	1.00	1.07 (0.85–1.35)	1.15 (0.89–1.48)	1.28 (1.02–1.61)	1.28 (0.98–1.67)	0.02	1.08 (1.02–1.14)
Advanced PC[b]	Cases	162	246	172	279	157		
	MV-adj RR[a]	1.00	1.15 (0.93–1.42)	1.16 (0.93–1.45)	1.30 (1.06–1.60)	1.29 (1.02–1.64)	0.008	1.08 (1.02–1.13)
Non-advanced PC[b]	Cases	625	939	735	1046	645		
	MV-adj RR[a]	1.00	1.00 (0.90–1.11)	1.04 (0.93–1.16)	0.96 (0.86–1.07)	0.96 (0.86–1.08)	0.32	0.99 (0.97–1.02)
Gleason 8–10 PC	Cases	115	167	130	183	112		
	MV-adj RR[a]	1.00	1.03 (0.81–1.33)	1.13 (0.87–1.48)	1.01 (0.79–1.29)	1.07 (0.81–1.42)	0.78	1.02 (0.96–1.08)
Gleason 7 PC	Cases	250	413	293	486	334		
	MV-adj RR[a]	1.00	1.13 (0.96–1.32)	1.06 (0.89–1.27)	1.13 (0.97–1.33)	1.24 (1.04–1.47)	0.02	1.05 (1.01–1.09)
Gleason 2–6 PC	Cases	404	603	474	632	363		
	MV-adj RR[a]	1.00	0.97 (0.85–1.10)	1.03 (0.89–1.18)	0.88 (0.78–1.01)	0.83 (0.72–0.97)	0.004	0.96 (0.93–0.99)

[a]Relative risks (RR) are hazard ratios with 95 % confidence intervals derived from Cox proportional hazards regression models. All models are multivariable (MV)-adjusted for age in months, calendar time, ethnicity (White, African-American, Asian-American, other), vigorous activity (0 MET-h/w; 0.1–3.4; 3.5–10.4; 10.5–28.4; ≥28.5), energy intake (continuous), smoking (never smoker; past smoker, quit >10 yrs ago; past smoker, quit ≤10 yrs ago; current smoker), diabetes (yes/no), family history of prostate cancer (father or brother, yes/no), prostate-specific antigen (PSA) test (yes/no, collected from 1994 onwards; lagged one period to avoid counting diagnostic tests as screening), and PSA intensity (PSA test in < or > 50% of periods, lagged one period). *P* values are derived from χ^2 test for trend across exposure categories (α=0.05). Age-adjusted models showed little differences.

[b] Lethal prostate cancer: Death due to prostate cancer or distant metastases at diagnosis or during follow-up. Advanced: T3b/T4 or N1 or M1 at diagnosis, lethal, or any metastases during follow-up. Non-advanced: T1/T2 and N0 and M0 at diagnosis, no metastases or death due to prostate cancer during follow-up.

Table 3

Relative risk of prostate cancer (PC) in relation to body mass index (BMI) at age 21 in the Health Professionals Follow-up Study (1986–2010)

		Body mass index at age 21 (kg/m^2)						
		<20	**20–21.9**	**22–23.9**	**24–25.9**	**≥26**	**P_{trend}**	**Continuous per 5 kg/m^2**
Total PC	Cases	825	1546	1852	1132	588		
	MV-adj RR[a]	0.99 (0.90–1.08)	1.00	0.98 (0.91–1.05)	0.92 (0.85–1.00)	0.89 (0.80–0.98)	0.01	0.94 (0.89–0.98)
Fatal PC	Cases	94	181	177	88	51		
	MV-adj RR[a]	0.83 (0.64–1.07)	1.00	0.92 (0.74–1.14)	0.74 (0.57–0.97)	0.77 (0.56–1.07)	0.20	0.88 (0.75–1.02)
Lethal PC[b]	Cases	118	231	223	118	63		
	MV-adj RR[a]	0.82 (0.65–1.03)	1.00	0.90 (0.74–1.09)	0.77 (0.61–0.96)	0.73 (0.55–0.98)	0.12	0.88 (0.76–1.00)
Advanced PC[b]	Cases	150	290	300	155	81		
	MV-adj RR[a]	0.86 (0.70–1.06)	1.00	0.92 (0.78–1.09)	0.77 (0.62–0.94)	0.69 (0.53–0.89)	0.01	0.85 (0.76–0.96)
Non-advanced PC[b]	Cases	537	970	1176	774	389		
	MV-adj RR[a]	1.04 (0.93–1.16)	1.00	0.97 (0.89–1.06)	0.96 (0.87–1.06)	0.91 (0.81–1.03)	0.05	0.93 (0.88–0.99)
Gleason 8–10 PC	Cases	85	181	204	130	79		
	MV-adj RR[a]	0.82 (0.63–1.07)	1.00	0.93 (0.75–1.15)	0.91 (0.72–1.16)	1.10 (0.83–1.45)	0.27	1.03 (0.90–1.19)
Gleason 7 PC	Cases	233	446	548	333	159		
	MV-adj RR[a]	0.98 (0.83–1.15)	1.00	0.98 (0.86–1.11)	0.90 (0.78–1.04)	0.77 (0.64–0.93)	0.01	0.87 (0.80–0.95)
Gleason 2–6 PC	Cases	333	620	735	465	236		
	MV-adj RR[a]	1.01 (0.88–1.16)	1.00	0.94 (0.84–1.05)	0.90 (0.79–1.02)	0.88 (0.75–1.03)	0.03	0.93 (0.87–1.01)

[a]Relative risks (RR) are hazard ratios with 95 % confidence intervals derived from Cox proportional hazards regression models. All models are multivariable (MV)-adjusted for age in months, calendar time, ethnicity (White, African-American, Asian-American, other), vigorous activity (0 MET-h/w; 0.1–3.4; 3.5–10.4; 10.5–28.4; ≥28.5), energy intake (continuous), smoking (never smoker; past smoker, quit >10 yrs ago; past smoker, quit ≤10 yrs ago; current smoker), diabetes (yes/no), family history of prostate cancer (father or brother, yes/no), prostate-specific antigen (PSA) test (yes/no, collected from 1994 onwards; lagged one period to avoid counting diagnostic tests as screening), and PSA intensity (PSA test in < or > 50% of periods, lagged one period). *P* values are derived from χ^2 test for trend across exposure categories (α=0.05). Age-adjusted models showed little differences.

[b] Lethal prostate cancer: Death due to prostate cancer or distant metastases at diagnosis or during follow-up. Advanced: T3b/T4 or N1 or M1 at diagnosis, lethal, or any metastases during follow-up. Non-advanced: T1/T2 and N0 and M0 at diagnosis, no metastases or death due to prostate cancer during follow-up.

Table 4

Relative risk of prostate cancer (PC) in relation to body mass index (BMI), cumulative average since 1988, stratified by age, in the Health Professionals Follow-up Study (1988–2010)

		Body mass index, cumulative average since 1988, lagged two years (kg/m^2)							
		<21	**21–22.9**	**23–24.9**	**25–27.4**	**27.5–29.9**	**≥30**	**P_{trend}**	**Continuous per 5 kg/m^2**
Total PC									
Age ≤65 y	Cases	65	280	557	576	297	147		
	MV-adj RR[a]	1.11 (0.84–1.48)	1.00	0.90 (0.78–1.05)	0.81 (0.70–0.94)	0.81 (0.68–0.96)	0.64 (0.51–0.78)	<0.001	0.83 (0.76–0.89)
Age >65 y	Cases	114	550	1188	1333	605	335		
	MV-adj RR[a]	0.87 (0.70–1.07)	1.00	1.07 (0.96–1.19)	1.04 (0.93–1.15)	1.04 (0.92–1.18)	0.97 (0.84–1.12)	0.99	0.99 (0.94–1.05)
Fatal PC									
Age ≤65 y	Cases	6	22	38	38	16	14		
	MV-adj RR[a]	1.32 (0.52–3.35)	1.00	0.81 (0.47–1.40)	0.68 (0.39–1.17)	0.60 (0.31–1.17)	0.83 (0.41–1.69)	0.21	0.92 (0.70–1.22)
Age >65 y	Cases	15	70	127	134	64	34		
	MV-adj RR[a]	0.77 (0.43–1.37)	1.00	0.95 (0.70–1.29)	0.96 (0.71–1.31)	1.05 (0.73–1.50)	1.06 (0.68–1.64)	0.43	1.03 (0.88–1.20)
Lethal PC[b]									
Age ≤65 y	Cases	7	28	54	51	23	17		
	MV-adj RR[a]	1.17 (0.50–2.73)	1.00	0.89 (0.55–1.43)	0.72 (0.45–1.17)	0.66 (0.37–1.18)	0.83 (0.44–1.57)	0.19	0.96 (0.75–1.21)
Age >65 y	Cases	22	85	160	165	83		39	
	MV-adj RR[a]	0.87 (0.53–1.43)	1.00	0.98 (0.74–1.29)	0.94 (0.71–1.24)	1.08 (0.78–1.48)	0.91 (0.61–1.35)	0.92	0.99 (0.86–1.14)
Advanced PC[b]									
Age ≤65 y	Cases	13	38	76	87	32	23		
	MV-adj RR[a]	1.59 (0.83–3.04)	1.00	0.93 (0.62–1.39)	0.88 (0.59–1.30)	0.66 (0.40–1.08)	0.79 (0.46–1.37)	0.04	0.88 (0.71–1.08)
Age >65 y	Cases	23	107	198	209	101	45		
	MV-adj RR[a]	0.75 (0.46–1.21)	1.00	0.95 (0.74–1.21)	0.91 (0.71–1.16)	0.99 (0.74–1.32)	0.75 (0.52–1.08)	0.50	0.94 (0.82–1.07)
Non-advanced PC[b]									
Age ≤65 y	Cases	46	200	388	373	197	93		

		Body mass index, cumulative average since 1988, lagged two years (kg/m^2)							
		<21	**21–22.9**	**23–24.9**	**25–27.4**	**27.5–29.9**	**≥30**	**P_{trend}**	**Continuous per 5 kg/m^2**
	MV-adj RR[a]	1.11 (0.79–1.55)	1.00	0.87 (0.73–1.04)	0.73 (0.61–0.88)	0.75 (0.61–0.93)	0.57 (0.44–0.74)	<0.001	0.79 (0.71–0.87)
Age >65 y	Cases	69	357	777	848	381	214		
	MV-adj RR[a]	0.84 (0.65–1.10)	1.00	1.07 (0.94–1.22)	0.99 (0.87–1.13)	0.99 (0.85–1.15)	0.93 (0.78–1.11)	0.43	0.96 (0.90–1.02)
Gleason 8–10 PC									
Age ≤65 y	Cases	8	27	48	53	30	17		
	MV-adj RR[a]	1.45 (0.64–3.29)	1.00	0.82 (0.50–1.35)	0.76 (0.46–1.23)	0.81 (0.47–1.39)	0.74 (0.39–1.42)	0.23	0.93 (0.73–1.17)
Age >65 y	Cases	16	57	157	149	81	49		
	MV-adj RR[a]	1.04 (0.58–1.85)	1.00	1.40 (1.02–1.92)	1.18 (0.86–1.61)	1.41 (0.99–2.01)	1.39 (0.93–2.09)	0.18	1.12 (0.97–1.28)
Gleason 7 PC									
Age ≤65 y	Cases	29	88	207	192	89	42		
	MV-adj RR[a]	1.70 (1.10–2.62)	1.00	1.08 (0.84–1.39)	0.87 (0.67–1.12)	0.77 (0.57–1.05)	0.57 (0.39–0.83)	<0.001	0.72 (0.63–0.83)
Age >65 y	Cases	32	147	324	349	167	83		
	MV-adj RR*	0.96 (0.65–1.43)	1.00	1.10 (0.90–1.35)	1.02 (0.83–1.24)	1.04 (0.82–1.31)	0.86 (0.65–1.14)	0.29	0.91 (0.83–1.01)
Gleason 2–6 PC									
Age ≤65 y	Cases	24	141	235	251	122	61		
	MV-adj RR[a]	0.77 (0.49–1.22)	1.00	0.75 (0.61–0.94)	0.73 (0.58–0.90)	0.69 (0.54–0.89)	0.57 (0.41–0.78)	0.0015	0.82 (0.73–0.93)
Age >65 y	Cases	40	218	472	535	211	127		
	MV-adj RR[a]	0.76 (0.54–1.08)	1.00	1.04 (0.88–1.23)	0.99 (0.84–1.16)	0.89 (0.73–1.08)	0.91 (0.72–1.14)	0.32	0.94 (0.87–1.03)

[a]Relative risks (RR) are hazard ratios with 95 % confidence intervals derived from Cox proportional hazards regression models. All models are multivariable (MV)-adjusted for age in months, calendar time, ethnicity (White, African-American, Asian-American, other), vigorous activity (0 MET-h/w; 0.1–3.4; 3.5–10.4; 10.5–28.4; ≥28.5), energy intake (continuous), smoking (never smoker; past smoker, quit >10 yrs ago; past smoker, quit ≤10 yrs ago; current smoker), diabetes (yes/no), family history of prostate cancer (father or brother, yes/no), prostate-specific antigen (PSA) test (yes/no, collected from 1994 onwards; lagged one period to avoid counting diagnostic tests as screening), and PSA intensity (PSA test in < or > 50% of periods, lagged one period). *P* values are derived from χ^2 test for trend across exposure categories (α=0.05). Age-adjusted models showed little differences.

[b]Lethal prostate cancer: Death due to prostate cancer or distant metastases at diagnosis or during follow-up. Advanced: T3b/T4 or N1 or M1 at diagnosis, lethal, or any metastases during follow-up. Non-advanced: T1/T2 and N0 and M0 at diagnosis, no metastases or death due to prostate cancer during follow-up.

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Table 5

Relative risk of prostate cancer (PC) in relation to body shape at age 10 in the Health Professionals Follow-up Study (1988–2010)

		Body shape at age 10[a]						
		Silhouette 1	**Silhouette 2**	**Silhouette 3**	**Silhouette 4**	**Silhouette 5**	**Silhouette 6–9**	**P_{trend}**
Total PC	Cases	1251	1516	802	454	316	332	
	MV-adj RR[b]	1.08 (1.00–1.17)	1.00	1.02 (0.93–1.11)	0.95 (0.85–1.06)	0.87 (0.77–0.99)	0.95 (0.84–1.08)	0.0014
Fatal PC	Cases	120	150	68	35	42	20	
	MV-adj RR[b]	1.02 (0.79–1.31)	1.00	0.98 (0.72–1.33)	0.83 (0.56–1.23)	1.46 (1.01–2.11)	0.82 (0.50–1.34)	0.91
Lethal PC[c]	Cases	168	183	85	47	47	30	
	MV-adj RR[b]	1.17 (0.94–1.46)	1.00	0.97 (0.74–1.28)	0.92 (0.65–1.29)	1.27 (0.91–1.79)	0.99 (0.66–1.49)	0.57
Advanced PC[c]	Cases	212	240	126	62	58	38	
	MV-adj RR[b]	1.11 (0.91–1.34)	1.00	1.07 (0.85–1.34)	0.88 (0.66–1.18)	1.07 (0.79–1.44)	0.84 (0.59–1.20)	0.18
Non-advanced PC[c]	Cases	841	1006	548	315	199	231	
	MV-adj RR[b]	1.11 (1.01–1.22)	1.00	1.05 (0.94–1.16)	0.97 (0.85–1.11)	0.80 (0.69–0.94)	0.95 (0.82–1.10)	0.0010
Gleason 8–10 PC	Cases	137	175	96	58	45	37	
	MV-adj RR[b]	0.98 (0.78–1.24)	1.00	1.05 (0.81–1.36)	1.04 (0.76–1.42)	1.14 (0.81–1.59)	1.04 (0.72–1.50)	0.47
Gleason 7 PC	Cases	381	413	248	145	87	102	
	MV-adj RR[b]	1.20 (1.04–1.39)	1.00	1.15 (0.97–1.35)	1.12 (0.92–1.36)	0.87 (0.68–1.10)	0.98 (0.78–1.22)	0.05
Gleason 2–6 PC	Cases	519	668	325	185	129	142	
	MV-adj RR[b]	1.05 (0.93–1.18)	1.00	0.94 (0.82–1.08)	0.85 (0.72–1.01)	0.76 (0.62–0.92)	0.90 (0.74–1.08)	<0.001

[a] Based on pictogram in Fig. 1.mol

[b] Relative risks (RR) are hazard ratios with 95 % confidence intervals derived from Cox proportional hazards regression models. All models are multivariable (MV)-adjusted for age in months, calendar time, ethnicity (White, African-American, Asian-American, other), vigorous activity (0 MET-h/w; 0.1–3.4; 3.5–10.4; 10.5–28.4; ≥28.5), energy intake (continuous), smoking (never smoker; past smoker, quit >10 yrs ago; past smoker, quit ≤10 yrs ago; current smoker), diabetes (yes/no), family history of prostate cancer (father or brother, yes/no), prostate-specific antigen (PSA) test (yes/no, collected from 1994 onwards; lagged one period to avoid counting diagnostic tests as screening), and PSA intensity (PSA test in < or > 50% of periods, lagged one period). *P* values are derived from χ^2 test for trend across exposure categories (α=0.05). Age-adjusted models showed little differences.

[c] Lethal prostate cancer: Death due to prostate cancer or distant metastases at diagnosis or during follow-up. Advanced: T3b/T4 or N1 or M1 at diagnosis, lethal, or any metastases during follow-up. Non-advanced: T1/T2 and N0 and M0 at diagnosis, no metastases or death due to prostate cancer during follow-up.