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Measures of Body Fatness and Height in Early and Mid-to-Late Adulthood and Prostate Cancer Risk and Mortality in the Pooling Project of Prospective Studies of Diet and Cancer

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Abstract

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Background: Advanced prostate cancer etiology is poorly understood. Few studies have examined associations of anthropometric factors (e.g., early adulthood obesity) with advanced prostate cancer risk.

Patients and Methods: We performed pooled analyses to examine associations between body fatness, height and prostate cancer risk. Among 830,772 men, 51,734 incident prostate cancer cases were identified, including 4,762 advanced (T4/N1/M1 or prostate cancer deaths) cases, 2,915 advanced restricted (same as advanced, but excluding localized cancers that resulted in death) cases, 9,489 high grade cases, and 3,027 prostate cancer deaths. Cox proportional hazards models were used to calculate study-specific hazard ratios (HR) and 95% confidence intervals (CI); results were pooled using random effects models.

Results: No statistically significant associations were observed for BMI in early adulthood for advanced, advanced restricted, and high-grade prostate cancer and prostate cancer mortality. Positive associations were shown for BMI at baseline with advanced prostate cancer (HR=1.30, 95% CI=0.95-1.78) and prostate cancer mortality (HR=1.52, 95% CI=1.12-2.07) comparing BMI≥35.0kg/m^2 with 21-22.9kg/m^2. When considering early adulthood and baseline BMI together, a 27% higher prostate cancer mortality risk (95% CI=9-49%) was observed for men with BMI<25.0kg/m^2 in early adulthood and BMI≥30.0kg/m^2 at baseline compared to BMI<25.0kg/m^2 in early adulthood and BMI<30.0kg/m^2 at baseline. Baseline waist circumference, comparing ≥110cm with <90cm, and waist-to-hip ratio, comparing ≥1.00 with <0.90, were associated with significant 14-16% increases in high-grade prostate cancer risk and suggestive or significant 20-39% increases in prostate cancer mortality risk. Height was associated with suggestive or significant 33-56% risks of advanced or advanced restricted prostate cancer and prostate cancer mortality, comparing ≥1.90m with <1.65m.

Conclusion: Our findings suggest that height and total and central adiposity in mid-to-later adulthood, but not early adulthood adiposity, are associated with risk of advanced forms of prostate cancer. Thus, maintenance of healthy weight may help prevent advanced prostate cancer.

Keywords

Prostate Cancer; Height; Body Fatness; BMI; waist; Pooled Analysis

Introduction

Worldwide, prostate cancer is the second most common cancer in men[1]. Over the past two decades, there has been a shift to diagnosis of earlier stage, indolent disease[2], largely attributed to widespread testing with prostate specific antigen (PSA). Unlike early stage prostate cancer, advanced prostate cancer (defined here as distant prostate cancer) has a markedly different prognosis with a 29% five-year survival, making advanced prostate cancer the most clinically relevant outcome[3]. Further, risk factors for high risk phenotypes may differ from those for low-risk tumors[4, 5]. Earlier studies of advanced prostate cancer have used various definitions for advanced prostate cancer (*e.g.*, high-grade, advanced stage, fatal). Due to these factors, evidence of risks for advanced prostate cancer is inconsistent and limited.

In 2018, an expert panel for the World Cancer Research Fund (WCRF) [6], determined that the level of evidence was probable for a positive association between height and body fatness and risk of advanced/aggressive forms of prostate cancer. In the WCRF meta-analysis, a 4% increase in risk of advanced prostate cancer and prostate specific mortality was observed for a 5 cm increment in height and an 8-11% increase in risk of advanced prostate cancer and prostate specific mortality was observed for a 5kg/m^2 increment in BMI[6]. In contrast, an International Agency for Research on Cancer (IARC) working group concluded in 2016 that the evidence for an association between body fatness and fatal prostate cancer was limited; other advanced/aggressive prostate cancer outcomes were not evaluated[7]. Thus, questions remain concerning the role of body fatness on the risk of prostate cancer, particularly for different definitions of advanced/aggressive prostate cancer.

Few studies have examined the associations of obesity earlier in life, changes in weight during adulthood, and central adiposity, typically measured in mid-to-late adulthood, with advanced prostate cancer risk. Of the six studies that have examined BMI or weight at younger adult ages (18-21 years old) and advanced or aggressive prostate cancer[8–13], most[8–11] observed null associations. Most studies examining central adiposity (*e.g.*, waist circumference) also have reported non-significant associations with advanced prostate cancer[14–20]. However, a meta-analysis of four studies noted a 12% (95% CI=4-21%) increase in risk of advanced prostate cancer per 10 cm increment in waist circumference[6]; a similar 18% increase in risk for prostate cancer death for the same increment was noted recently in the EPIC cohort[21]. Due to the relatively smaller number of advanced/aggressive cases in most studies (n<500), and heterogeneity in outcome definitions across studies, uncertainty remains about the strength and dose-response relationships of these anthropometric measures overall, as well as among certain subgroups (*e.g.*, younger ages, non-diabetics). Further, few studies of obesity have accounted for measures at both younger ages and mid-to-late adulthood in the same analysis[11, 12, 22], or have assessed if the associations observed with central adiposity [15, 18, 21] were independent of BMI.

To address these issues, we examined associations of obesity across the adult lifecourse and central adiposity in mid-to-late adulthood and adult height with risk of advanced and aggressive prostate cancer and prostate cancer mortality and compared these findings to risk of total, localized, and low grade cancers in one of the largest pooled analyses of individual level data.

Methods

Population

A pooled analysis of the primary data from 15 cohort studies[8, 9, 11, 12, 18, 21, 23–30] was conducted within The Pooling Project of Prospective Studies of Diet and Cancer (DCPP), an international consortium (Table 1). The current analysis used cohort inclusion criteria that have been used for previous analyses of dietary factors in the DCPP[31]: (1) a minimum of 50 incident prostate cancer cases, (2) an assessment of usual diet, (3) validation of the dietary assessment tool or a closely related instrument and (4) publication of any diet and cancer association; these inclusions were employed to maximize the quality and comparability of the studies in the consortium[32]. The cohorts that met our inclusion

criteria and agreed to participate sent their primary participant-level data for analysis[8, 9, 11, 12, 18, 21, 23–30]. For one cohort (the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial)[30], only participants in the screened arm were included[33], whereas for the Prostate Cancer Prevention Trial (PCPT) both arms were included. The DCPP methods have been described in detail elsewhere[32].

Exposure Assessment

Self-reported current height and weight, typically at mid-to-late adulthood, were collected at baseline by 10 cohorts; height and weight were measured in five cohorts [18, 19, 21, 23, 24]. Self-reported weight during early adulthood (18- 21 years of age) was collected by 11 cohorts. Seven cohorts collected waist and/or hip circumference, typically at mid-to-late adulthood. In these cohorts, waist and/or hip circumference was measured by study personnel [8, 18, 21] or by the participants themselves [11, 12, 26, 27]. At baseline, smoking habits were ascertained by all cohorts, physical activity was ascertained by 13 cohorts, and diabetes status was ascertained by 10 cohorts.

Outcome Assessment

Invasive prostate cancer, defined by ICD-9 code 185, was ascertained by self-report with subsequent medical record review [12, 24, 28], cancer registry linkage[9, 11, 25, 27, 29], or both methods[16, 23, 26, 30]. Some studies additionally obtained information from death registries [9, 11, 12, 16, 24–26, 28, 30]. For the Prostate Cancer Prevention Trial (PCPT)[18] only cases diagnosed through a biopsy performed because of an elevated PSA or abnormal digital-rectal examination suspicious for cancer were included as cases. Due to inconsistency in the literature regarding definitions for aggressive and advanced prostate cancer, and to better understand possible differences in the etiology of latent, advanced, aggressive and prostate cancer mortality, we classified advanced and aggressive prostate cancer cases and prostate cancer mortality as follows: (1) prostate cancer mortality cases, defined as prostate cancer that was the underlying cause of death on the death certificate, (2) advanced cases, defined as tumors with stage T4, N1, M1 or prostate cancer mortality cases, (3) advanced restricted cases, defined the same as for advanced cases but excluding prostate cancer mortality cases that were initially diagnosed as having localized prostate cancer or cases with missing stage information at diagnosis who died of prostate cancer during follow-up, and (4) high-grade cancers defined as having Gleason score ≥8 (within CARET, CLUE II, COSM, CPS II, EPIC, HPFS, JPHC I, JPHC II, MCCS, PCPT, PLCO) or being poorly differentiated / undifferentiated (within ATBC, CLUE II, CPS II, EPIC, JPHC I, JPHC II, MEC, MCCS, NIH-AARP, NLCS, PLCO) (see the Appendix in Wu et al.[31] for more detail). As a sensitivity analysis, we also examined a more restrictive definition of high-grade cancer that excluded poorly differentiated cases with Gleason score ≤7 or with missing Gleason score; this analysis was restricted to five cohorts [8, 21, 25, 26, 30] that had the necessary data (N=1,348 out of 2,265 high-grade cases were included in this analysis). We also included results for total, localized (defined as cancer confined within the prostate), and low-grade (defined as having a Gleason score <8 or well/moderately differentiated) prostate cancer for comparison.

Exclusions

In addition to predefined study-specific exclusions, we excluded individuals with (1) $\log_e$-transformed self-reported energy intakes beyond three standard deviations from the $\log_e$-transformed mean energy intake of their respective cohort population (because we conducted these analyses in the study populations used in dietary analyses in the consortium) and (2) a history of cancer other than non-melanoma skin cancer at baseline. After these exclusions, we additionally excluded men (3) missing weight or height data (N=906 cases, N= 10,531 non-cases), or (4) a BMI ≤14kg/m^2 (*N*=23 cases, *N*=319 non-cases) or ≥50kg/m^2 (*N*=20 cases, *N*=527 non-cases). For analyses of sub-types of prostate cancer, studies were excluded if they had fewer than 50 cases of the outcome being evaluated.

Statistical Analysis

Anthropometric measures were modeled both continuously and categorically. For the categorical analysis, BMI at baseline and BMI in early adulthood were modeled using cutpoints proposed by the World Health Organization[34]. Absolute BMI change (BMI at baseline, typically measured at mid-to-late adulthood, minus BMI in early adulthood) was categorized as:<−2.0, −2.0-<2.0, 2.0-<5.0, 5.0-<10.0, ≥10.0kg/m^2. Waist circumference categories were defined using 10-cm increments, waist-to-hip ratio categories were defined using 0.05 increments, and height was modeled categorically using 5cm increments.

For the prostate cancer incidence analyses, person-years of follow-up were calculated from the date of baseline questionnaire until the date of prostate cancer diagnosis, death from another cause, loss to follow-up or end of follow-up, whichever came first. For analyses of prostate cancer mortality, date of prostate cancer death was used instead of date of prostate cancer diagnosis. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated by fitting Cox proportional hazards regression models for each cohort. The models included stratification by age (years) at baseline and the calendar year at start of follow-up, and the time scale used was follow-up time (days). Multivariable-adjusted hazard ratios (MVHR) were adjusted for the following factors collected at baseline: race, education, marital status, alcohol intake, smoking habits, prostate cancer family history, personal history of diabetes, multivitamin use, and dietary calcium (from foods only), dietary lycopene (from foods only), and total energy intake. These variables were entered directly into the multivariable-adjusted model or, for studies with fewer than 200 cases, were modeled using propensity scores[35–37]. For models in which height was not the main exposure, height was included as a covariate in the model. For models in which height was the main exposure, we additionally adjusted for BMI at baseline. For models in which BMI in early adulthood, waist circumference, hip circumference or waist-to-hip ratio was the main exposure, we conducted sensitivity analyses in which BMI at baseline was included as a covariate in the model to examine the independent effects of each exposure. This approach also allowed examination of the mediational effects of BMI at baseline on the associations between BMI in early adulthood and risk of prostate cancer outcomes. For models in which absolute BMI change was the main exposure, we conducted sensitivity analyses in which we included BMI in early adulthood as a covariate in the model.

Study-specific HRs were pooled using a random effects model[32]. Between-studies heterogeneity was evaluated using the Q statistic[38] and inconsistency was quantified by the I^2 statistic[39]. We also evaluated whether each anthropometric factor was linearly associated with prostate cancer risk using non-parametric regression analyses in an aggregated data set in which the individual level data from each study were combined into a single dataset. To test for non-linearity, we used a likelihood ratio test to compare the model fit including the linear plus any cubic spline terms selected by a stepwise regression procedure with the model fit with only the linear term [40–42]. To test for a linear trend in prostate cancer risk with each anthropometric factor, a continuous variable with values corresponding to the median value for each exposure category was included in the model; the statistical significance of the coefficient for that variable was evaluated using the Wald test. Overall, results were similar between age-adjusted and multivariable-adjusted models, as well as from analyses of aggregated datasets (a dataset in which the individual level data from each study is combined into a single dataset) and analyses using a two stage approach; therefore, we only present multivariable-adjusted results using a two-stage approach, unless otherwise noted.

We used a mixed effects meta-regression model to evaluate whether associations with anthropometric factors varied by geographic location (North America compared with Europe, Asia, and Australia), age at diagnosis (<60 vs. ≥60 years), smoking status (comparing never, former, and current smokers), physical activity (comparing low, medium, and high activity) and follow-up time (<5 vs. ≥5 years). We conducted sensitivity analyses excluding 1) individuals with a personal history of diabetes at baseline, and 2) studies with PSA screening (PLCO and PCPT) as part of their protocol. To examine differences by case definition, we employed a contrast test[43]. A *p-value* of 0.05 from a two-sided test was considered statistically significant. SAS software, version 9.4, was used.

RESULTS

During follow-up of 830,772 men, 51,734 men were diagnosed with incident prostate cancer (Table 1), including 4,762 advanced cases, 2,915 advanced restricted cases, and 9,489 high-grade cases. The median BMI in early adulthood, reported for ages 18 to 21 years, ranged from 21.4kg/m^2 in NIH-AARP to 22.9kg/m^2 in HPFS, while BMI at baseline, primarily measured in mid-to-late adulthood, ranged from 23.4kg/m^2 in JPHC I/II to 27.7kg/m^2 in CARET (Table 2).

For BMI in early adulthood, we observed null associations for all forms of advanced / aggressive prostate cancer risk (advanced, advanced restricted, high grade prostate cancer) and prostate cancer mortality and statistically significant 6-9% lower risks for total, localized and low-grade prostate cancers when comparing BMI ≥ 25.0kg/m^2 with 21.0-22.9kg/m^2 (Table 3). Results were similar when we additionally adjusted for BMI at baseline, suggesting no strong mediational effects of BMI at baseline (Supplemental Table 1).

We observed statistically significant differences in risk associated with BMI at baseline, typically measured at mid-to-late adulthood, for advanced prostate cancer and prostate cancer mortality compared with localized tumors, and by grade (*p-value*, test for common

effects ≤0.01; Table 3). High BMI (≥35.0kg/m^2) compared with healthy BMI (21.0-22.9kg/m^2) at baseline was associated with 16-19% lower risks of localized and low-grade prostate cancers. In contrast, we observed positive, and significant, associations for advanced prostate cancer (HR=1.30, 95% CI=0.95-1.78; *p-value*, test for trend=0.01) and prostate cancer mortality (HR=1.52, 95% CI=1.12-2.07; *p-value*, test for trend<0.01) for the same comparison. When BMI at baseline was modeled as a continuous variable, statistically significant 7-10% increases in risk for both outcomes were observed for a 5kg/m^2 increment. Results were similar when we limited the analyses to those studies that also measured BMI in early adulthood (data not shown).

Total, localized and low-grade prostate cancer risk was statistically significantly 6-15% lower for those who were obese at baseline (BMI≥30.0kg/m^2) regardless of whether or not they were overweight in early adulthood (BMI≥25.0kg/m^2) compared with men reporting a BMI<25.0kg/m^2 in early adulthood and a BMI<30.0kg/m^2 at baseline (Table 3). A 27% higher risk for prostate cancer mortality (95% CI=9-49%) was observed for men who had a healthy BMI (<25.0kg/m^2) in early adulthood and were obese at baseline (BMI≥30.0kg/m^2), compared to men reporting a BMI<25.0kg/m^2 in early adulthood and a BMI<30.0kg/m^2 at baseline. A similar, but non-significant, risk (HR=1.20, 95% CI=0.95-1.52), was observed for men with a BMI>25.0kg/m^2 in early adulthood and a BMI>30.0kg/m^2 at baseline. No statistically significant associations were noted for any of the combined categories for BMI in early adulthood and BMI at baseline and risk of advanced, advanced restricted and high grade prostate cancer. No statistically significant differences in risk were noted across stage and grade. Results appeared consistent to these findings when we examined the absolute difference of BMI at baseline and BMI in early adulthood (Table 3); these results were similar when we adjusted for BMI in early adulthood (data not shown).

Waist circumference, typically measured in mid-to-late adulthood, was inversely associated with total (HR=0.95, 95% CI=0.90-1.00), localized (HR=0.93, 95% CI=0.88-0.99) and low-grade (HR=0.90, 95% CI=0.85-0.95) prostate cancer when comparing ≥110 with <90cm (Table 4). In contrast, we observed positive associations between waist circumference and prostate cancer mortality (comparing ≥110 with <90cm: HR=1.39, 95% CI=1.14-1.71) and high-grade prostate cancer (HR=1.16, 95% CI=1.03-1.31), and between waist-to-hip ratio and risk of high-grade prostate cancer (HR comparing ≥1.00 with <0.90=1.14, 95% CI=1.01-1.28). Overall, risk was similar when we adjusted for BMI at baseline (Supplemental table 1).

Height was associated with a higher risk of total, advanced, and advanced restricted prostate cancer, and prostate cancer mortality (Table 5); no statistically significant associations were observed for localized, low- or high-grade prostate cancer risk. Results were similar when we removed BMI at baseline as a covariate (data not shown).

For advanced and advanced restricted prostate cancer and prostate cancer mortality, results for most anthropometric factors were similar when we stratified by age at diagnosis and smoking habits (Supplemental table 2). Associations of baseline BMI and prostate cancer mortality, waist circumference and risk of advanced prostate cancer, and waist circumference and prostate cancer mortality appeared to differ among strata of physical activity (*p-value*,

tests for interaction ≤0.01), with positive associations suggested in the lowest (10-17% higher) and highest (20-23% higher) strata and null or inverse (12-16% lower) in the middle stratum of physical activity.

Results for anthropometric factors were similar when we excluded those with a personal history of diabetes (Supplemental table 2). As PSA testing has shifted the diagnosis to identification of mostly latent (or low-grade) disease[44–48] in places where the test has been in routine use, we examined results by geographic region. For all anthropometric factors, results were similar for studies conducted in North America, where widespread PSA testing began in 1992 (data not shown); in the countries of the remaining studies routine PSA testing, if adopted, was initiated later in time. As all participants in the PLCO trial [49] and the PCPT [50] who were included in this study underwent PSA testing routinely as part of the trial protocol, we repeated our analyses excluding these two studies and results were essentially unchanged (data not shown). Further, in analyses for high-grade prostate cancer in which we excluded cases with Gleason scores≤7 that were poorly differentiated or were missing Gleason scores, the results were similar to the main findings (data not shown). To evaluate lag effects, models were stratified by follow-up time; results were similar for <5 years compared with ≥5 years of follow-up time (Supplemental table 2).

DISCUSSION

In this pooled analysis of prospective cohorts, we observed positive associations for BMI at baseline (primarily mid-to-late adulthood) with risk of advanced prostate cancer and prostate cancer mortality, and for waist circumference (primarily in mid-to-late adulthood) and risk of high-grade prostate cancer and prostate cancer mortality. In contrast, we observed inverse associations with total, localized and low grade cancers for these anthropometric factors. Risk of prostate cancer mortality was also elevated for men with a healthy weight in early adulthood but who were obese at baseline. We also observed suggestive or statistically significant positive associations for waist-to-hip ratio and height with more aggressive/advanced forms of prostate cancer and prostate cancer mortality. Null or nonsignificant associations were noted for BMI in early adulthood, and hip circumference and risk of more advanced/aggressive forms of prostate cancer and prostate cancer mortality, but inverse associations were observed for localized and low grade prostate cancers. Overall, in comparison to the summary estimates published in the WCRF expert report, we observed similar positive associations for BMI at baseline, and height, and similar null associations for BMI in early adulthood. Although 10 cohorts included in our pooled analysis were also included in the WCRF meta-analysis for BMI at baseline and height, our study included five additional cohorts in the BMI at baseline and in early adulthood and height analyses [6]. Unlike previous studies, we systematically examined the association between anthropometric factors with the various outcome definitions for advanced (e.g., advanced stage), aggressive (e.g., high-grade) prostate cancers and prostate cancer mortality across studies. Our results are among the first to demonstrate that measures of central adiposity, independent of BMI, are associated with advanced forms of prostate cancer. Visceral adiposity may increase risk of advanced forms of prostate cancer through changes in cytokines and growth factors, hormone regulation and metabolism [51–56]. Our lack of an association for BMI in early adulthood may be due to the following factors: 1) early

adulthood may not be the critical window of exposure for prostate cancer risk; 2) the contrast between extreme categories for BMI in early adulthood was limited and we could not examine obese categories alone; and 3) survivor bias. However, the latter explanation is unlikely given we have observed positive associations with BMI in early adulthood with pancreatic cancer risk within the DCPP[57].

Many previous studies, that have examined risks for advanced forms of prostate cancer, have been limited in their ability to analyze population subgroups or to stratify by important risk factors for prostate cancer. In general, our results were consistent across strata of age and smoking and in non-diabetics. However, we observed statistically significant multiplicative interactions by physical activity for BMI at baseline and waist circumference with risk of advanced forms of prostate cancer. Our results were similar to three previous studies (including one study that is included in our analysis)[58] that observed differences in associations between BMI and prostate cancer risk by physical activity[58–60]. It has been hypothesized that physical activity may modify the BMI-prostate cancer association due to modification of hormone and metabolic pathways. Or, this finding may be the result of heterogeneity in measurement of physical activity across studies, heterogeneity in the fat and muscle mass distribution of men across different levels of physical activity, and/or reduced diagnostic effectiveness of PSA testing and digital-rectal examinations in obese men[58–62]. Given that we did not observe a discernable pattern, these results also could be due to chance.

A limited number of studies have examined associations between anthropometric factors and risk of aggressive and advanced subtypes of prostate cancer; many were generally limited by case numbers and statistical power. In addition, studies have applied different outcome definitions. As we pooled prospective data from 15 cohort studies, creating one of the largest pooled datasets to date, we had greater statistical power than any individual study to examine prostate cancer subtypes with regards to anthropometric measures. We harmonized the exposures, covariates and outcomes, along with the modeling approach, across individual studies, thereby reducing potential sources of heterogeneity across studies. In particular, our case definition included six subtypes of prostate cancer, defined uniformly across studies. Further, with adequate statistical power, we systematically examined whether these associations were modified by other prostate cancer risk factors.

For each cohort, anthropometric measures were collected prior to cancer diagnosis; thus, a cancer diagnosis was unlikely to influence the reporting of anthropometry as may occur in a case-control study. However, individuals who were diagnosed close in time to study enrollment may have already experienced changes in anthropometry due to pre-diagnostic disease; this would likely be limited to men who had very aggressive disease and likely would have had diagnosis at a distant metastatic stage. Reassuringly, results from analyses stratified by follow-up time were similar.

Although we cannot rule out uncontrolled confounding by unknown or unmeasured factors or residual confounding from measurement error in the included covariates, all studies collected information on established or suspected prostate cancer risk factors (*e.g.*, age, race, smoking history, physical activity) and the majority of studies collected diabetes history.

Although height and weight were self-reported in 10 cohorts, most studies have observed high correlations between self-reported and measured anthropometric factors[63, 64]; however, any misclassification of our exposures is likely to be non-differential which may result in our risk estimates being underestimated. In our analyses, we focused our exposures on baseline assessment, primarily assessed in mid-to-late adulthood and did not consider changes in anthropometric factors and covariates during follow-up time; thus, we may have some misclassification of our exposures and covariates over time. Our pooled analysis was unable to examine differences by race and ethnicity as most individuals in each cohort were non-Hispanic White. Further, we conducted multiple statistical tests and examined results in a number of subgroups and cannot rule out chance findings. On the other hand, the fact that our results were consistent across studies, and the cohorts in our analysis represent populations from different geographic regions with different age ranges and education levels and varied prevalence of PSA testing, adds to the robustness of our findings.

In summary, we observed positive associations of BMI, waist circumference and height, typically measured at mid-to-late adulthood, with risk of various definitions of advanced/aggressive forms of prostate cancer and prostate cancer mortality. However, measures of body fatness in early adulthood were not associated with risk of advanced prostate cancer and prostate cancer mortality. Thus, maintenance of healthy weight is important for prostate cancer risk as well as numerous other health conditions. Further, it is important to understand the underlying mechanism associated with measures of adiposity and height to reduce the morbidity and mortality associated with this and related diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Ferlay J, Soerjomataram I, Ervik M et al. Globocan 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. In. Lyon, France: International Agency for Research on Cancer 2013.
2. Howlader N, Noone AM, Krapcho M et al. SEER Cancer Statistics Review, 1975-2012, National Cancer Institute. In. Bethesda, MD: based on November 2014 SEER data submission, posted to the SEER web site, April 2015.
3. American Cancer Society. Cancer Facts and Figures 2017. In. Atlanta: American Cancer Society 2017.

4. Giovannucci E, Liu Y, Platz EA et al. Risk factors for prostate cancer incidence and progression in the health professionals follow-up study. Int J Cancer 2007; 121: 1571–1578. [PubMed: 17450530]
5. Jahn JL, Giovannucci EL, Stampfer MJ. The high prevalence of undiagnosed prostate cancer at autopsy: implications for epidemiology and treatment of prostate cancer in the Prostate-specific Antigen-era. Int J Cancer 2015; 137: 2795–2802. [PubMed: 25557753]
6. World Cancer Research Fund/American Institute for Cancer Research. Diet, Nutrition, Physical Activity and Cancer: a Global Perspective. Continuous Update Project Expert Report 2018. Available at dietandcancerreport.org. 2018.
7. Lauby-Secretan B, Scoccianti C, Loomis D et al. Body Fatness and Cancer--Viewpoint of the IARC Working Group. N Engl J Med 2016; 375: 794–798. [PubMed: 27557308]
8. Bassett JK, Severi G, Baglietto L et al. Weight change and prostate cancer incidence and mortality. Int J Cancer 2012; 131: 1711–1719. [PubMed: 22213024]
9. Hernandez BY, Park SY, Wilkens LR et al. Relationship of body mass, height, and weight gain to prostate cancer risk in the multiethnic cohort. Cancer Epidemiol Biomarkers Prev 2009; 18: 2413–2421. [PubMed: 19723920]
10. Littman AJ, White E, Kristal AR. Anthropometrics and prostate cancer risk. Am J Epidemiol 2007; 165: 1271–1279. [PubMed: 17395597]
11. Wright ME, Chang SC, Schatzkin A et al. Prospective study of adiposity and weight change in relation to prostate cancer incidence and mortality. Cancer 2007; 109: 675–684. [PubMed: 17211863]
12. Moller E, Wilson KM, Batista JL et al. Body size across the life course and prostate cancer in the Health Professionals Follow-up Study. Int J Cancer 2016; 138: 853–865. [PubMed: 26355806]
13. Kelly SP, Graubard BI, Andreotti G et al. Prediagnostic Body Mass Index Trajectories in Relation to Prostate Cancer Incidence and Mortality in the PLCO Cancer Screening Trial. J Natl Cancer Inst 2017; 109: 1–9.
14. Martin RM, Vatten L, Gunnell D et al. Components of the metabolic syndrome and risk of prostate cancer: the HUNT 2 cohort, Norway. Cancer Causes Control 2009; 20: 1181–1192. [PubMed: 19277881]
15. Wallstrom P, Bjartell A, Gullberg B et al. A prospective Swedish study on body size, body composition, diabetes, and prostate cancer risk. Br J Cancer 2009; 100: 1799–1805. [PubMed: 19436298]
16. Pischon T, Boeing H, Weikert S et al. Body size and risk of prostate cancer in the European prospective investigation into cancer and nutrition. Cancer Epidemiol Biomarkers Prev 2008; 17: 3252–3261. [PubMed: 18990768]
17. Baillargeon J, Platz EA, Rose DP et al. Obesity, adipokines, and prostate cancer in a prospective population-based study. Cancer Epidemiol Biomarkers Prev 2006; 15: 1331–1335. [PubMed: 16835332]
18. Gong Z, Neuhouser ML, Goodman PJ et al. Obesity, diabetes, and risk of prostate cancer: results from the prostate cancer prevention trial. Cancer Epidemiol Biomarkers Prev 2006; 15: 1977–1983. [PubMed: 17035408]
19. MacInnis RJ, English DR, Gertig DM et al. Body size and composition and prostate cancer risk. Cancer Epidemiol Biomarkers Prev 2003; 12: 1417–1421. [PubMed: 14693731]
20. Giovannucci E, Rimm EB, Stampfer MJ et al. Height, body weight, and risk of prostate cancer. Cancer Epidemiol Biomarkers Prev 1997; 6: 557–563. [PubMed: 9264267]
21. Perez-Cornago A, Appleby PN, Pischon T et al. Tall height and obesity are associated with an increased risk of aggressive prostate cancer: results from the EPIC cohort study. BMC Med 2017; 15: 115. [PubMed: 28701188]
22. Gray L, Lee IM, Sesso HD, Batty GD. Association of body mass index in early adulthood and middle age with future site-specific cancer mortality: the Harvard Alumni Health Study. Ann Oncol 2012; 23: 754–759. [PubMed: 21677311]
23. Ahn J, Moslehi R, Weinstein SJ et al. Family history of prostate cancer and prostate cancer risk in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study. Int J Cancer 2008; 123: 1154–1159. [PubMed: 18546266]

24. Neuhouser ML, Barnett MJ, Kristal AR et al. Dietary supplement use and prostate cancer risk in the Carotene and Retinol Efficacy Trial. Cancer Epidemiol Biomarkers Prev 2009; 18: 2202–2206. [PubMed: 19661078]
25. Chae YK, Huang HY, Strickland P et al. Genetic polymorphisms of estrogen receptors alpha and beta and the risk of developing prostate cancer. PLoS One 2009; 4: e6523. [PubMed: 19654868]
26. Rodriguez C, Freedland SJ, Deka A et al. Body mass index, weight change, and risk of prostate cancer in the Cancer Prevention Study II Nutrition Cohort. Cancer Epidemiol Biomarkers Prev 2007; 16: 63–69. [PubMed: 17179486]
27. Discacciati A, Orsini N, Andersson SO et al. Body mass index in early and middle-late adulthood and risk of localised, advanced and fatal prostate cancer: a population-based prospective study. Br J Cancer 2011; 105: 1061–1068. [PubMed: 21847119]
28. Inoue M, Sobue T, Tsugane S, JPHC Study Group. Impact of body mass index on the risk of total cancer incidence and mortality among middle-aged Japanese: data from a large-scale population-based cohort study--the JPHC study. Cancer Causes Control 2004; 15: 671–680. [PubMed: 15280625]
29. Schuurman AG, Goldbohm RA, Dorant E, van den Brandt PA. Anthropometry in relation to prostate cancer risk in the Netherlands Cohort Study. Am J Epidemiol 2000; 151: 541–549. [PubMed: 10733035]
30. Leitzmann MF, Ahn J, Albanes D et al. Diabetes mellitus and prostate cancer risk in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Cancer Causes Control 2008; 19: 1267–1276. [PubMed: 18618278]
31. Wu K, Spiegelman D, Hou T et al. Associations between unprocessed red and processed meat, poultry, seafood and egg intake and the risk of prostate cancer: A pooled analysis of 15 prospective cohort studies. Int J Cancer 2016; 138: 2368–2382. [PubMed: 26685908]
32. Smith-Warner SA, Spiegelman D, Ritz J et al. Methods for pooling results of epidemiologic studies: the Pooling Project of Prospective Studies of Diet and Cancer. Am J Epidemiol 2006; 163: 1053–1064. [PubMed: 16624970]
33. Prorok PC, Andriole GL, Bresalier RS et al. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Control Clin Trials 2000; 21: 273S–309S. [PubMed: 11189684]
34. Physical status: The Use and Interpretation of Anthropometry. Report of a WHO Expert Committee. In Committee WHOWE (ed) WHO Technical Report Series: 854, 1992. Geneva, Switzerland: World Health Organization 1995.
35. Cepeda MS. The use of propensity scores in pharmacoepidemiologic research. Pharmacoepidemiol Drug Saf 2000; 9: 103–104. [PubMed: 19025808]
36. Joffe MM, Rosenbaum PR. Invited commentary: propensity scores. Am J Epidemiol 1999; 150: 327–333. [PubMed: 10453808]
37. Imai K, van Dyk DA. Causal inference with general treatment regimes:generalizing the propensity score. J Am Stat Assoc 2004; 99: 854–866.
38. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials 1986; 7: 177–188. [PubMed: 3802833]
39. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21: 1539–1558. [PubMed: 12111919]
40. Govindarajulu US, Spiegelman D, Thurston SW et al. Comparing smoothing techniques in Cox models for exposure-response relationships. Stat Med 2007; 26: 3735–3752. [PubMed: 17538974]
41. Smith PL. Splines as a useful and convenient statistical tool. The American Statistician 1979; 33: 57–62.
42. Durrleman S, Simon R. Flexible regression models with cubic splines. Statistics in Medicine 1989; 8: 551–561. [PubMed: 2657958]
43. Wang M, Spiegelman D, Kuchiba A et al. Statistical methods for studying disease subtype heterogeneity. Stat Med 2016; 35: 782–800. [PubMed: 26619806]
44. Draisma G, Etzioni R, Tsodikov A et al. Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. J Natl Cancer Inst 2009; 101: 374–383. [PubMed: 19276453]

45. Draisma G, Boer R, Otto SJ et al. Lead times and overdetection due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. J Natl Cancer Inst 2003; 95: 868–878. [PubMed: 12813170]
46. Etzioni R, Penson DF, Legler JM et al. Overdiagnosis due to prostate-specific antigen screening: lessons from U.S. prostate cancer incidence trends. J Natl Cancer Inst 2002; 94: 981–990. [PubMed: 12096083]
47. Tsodikov A, Szabo A, Wegelin J. A population model of prostate cancer incidence. Stat Med 2006; 25: 2846–2866. [PubMed: 16397859]
48. McGregor M, Hanley JA, Boivin JF, McLean RG. Screening for prostate cancer: estimating the magnitude of overdetection. CMAJ 1998; 159: 1368–1372. [PubMed: 9861205]
49. Cross AJ, Peters U, Kirsh VA et al. A prospective study of meat and meat mutagens and prostate cancer risk. Cancer Res 2005; 65: 11779–11784. [PubMed: 16357191]
50. Kristal AR, Arnold KB, Neuhouser ML et al. Diet, supplement use, and prostate cancer risk: results from the prostate cancer prevention trial. Am J Epidemiol 2010; 172: 566–577. [PubMed: 20693267]
51. Allan CA, McLachlan RI. Androgens and obesity. Curr Opin Endocrinol Diabetes Obes 2010; 17: 224–232. [PubMed: 20418719]
52. Khaw KT, Barrett-Connor E. Lower endogenous androgens predict central adiposity in men. Ann Epidemiol 1992; 2: 675–682. [PubMed: 1342319]
53. Tsai EC, Boyko EJ, Leonetti DL, Fujimoto WY. Low serum testosterone level as a predictor of increased visceral fat in Japanese-American men. Int J Obes Relat Metab Disord 2000; 24: 485–491. [PubMed: 10805506]
54. Donohoe CL, Doyle SL, Reynolds JV. Visceral adiposity, insulin resistance and cancer risk. Diabetol Metab Syndr 2011; 3: 12. [PubMed: 21696633]
55. Himbert C, Delphan M, Scherer D et al. Signals from the Adipose Microenvironment and the Obesity-Cancer Link-A Systematic Review. Cancer Prev Res (Phila) 2017; 10: 494–506. [PubMed: 28864539]
56. Strong AL, Burow ME, Gimble JM, Bunnell BA. Concise review: The obesity cancer paradigm: exploration of the interactions and crosstalk with adipose stem cells. Stem Cells 2015; 33: 318–326. [PubMed: 25267443]
57. Genkinger JM, Spiegelman D, Anderson KE et al. A pooled analysis of 14 cohort studies of anthropometric factors and pancreatic cancer risk. Int J Cancer 2011; 129: 1708–1717. [PubMed: 21105029]
58. Zeegers MP, Dirx MJ, van den Brandt PA. Physical activity and the risk of prostate cancer in the Netherlands cohort study, results after 9.3 years of follow-up. Cancer Epidemiol Biomarkers Prev 2005; 14: 1490–1495. [PubMed: 15941961]
59. Grotta A, Bottai M, Adami HO et al. Physical activity and body mass index as predictors of prostate cancer risk. World J Urol 2015; 33: 1495–1502. [PubMed: 25557943]
60. Wiklund F, Lageros YT, Chang E et al. Lifetime total physical activity and prostate cancer risk: a population-based case-control study in Sweden. Eur J Epidemiol 2008; 23: 739–746. [PubMed: 18931922]
61. Deere K, Sayers A, Davey Smith G et al. High impact activity is related to lean but not fat mass: findings from a population-based study in adolescents. Int J Epidemiol 2012; 41: 1124–1131. [PubMed: 22576953]
62. Ekelund U, Besson H, Luan J et al. Physical activity and gain in abdominal adiposity and body weight: prospective cohort study in 288,498 men and women. Am J Clin Nutr 2011; 93: 826–835. [PubMed: 21346093]
63. Spencer EA, Appleby PN, Davey GK, Key TJ. Validity of self-reported height and weight in 4808 EPIC-Oxford participants. Public Health Nutr 2002; 5: 561–565. [PubMed: 12186665]
64. Rimm EB, Stampfer MJ, Colditz GA et al. Validity of self-reported waist and hip circumferences in men and women. Epidemiology 1990; 1: 466–473. [PubMed: 2090285]

KEY MESSAGE:

Few have examined the role of early adulthood BMI and adult BMI changes on advanced forms of prostate cancer risk. We reported positive associations of height, BMI and waist circumference in mid-to-late adulthood, and adult BMI change with advanced forms of prostate cancer risk and prostate cancer mortality, but no significant associations for BMI in early adulthood.

Table 1.

Baseline Characteristics of Studies included in the Pooled Analysis for Anthropometry and Risk of Prostate Cancer Incidence and Mortality

					Prostate Cancer Cases (*N*)						
Cohort[1]	**Country**	**Follow-up Time (Median)**	**Baseline cohort size**[2,3]	**Median Age (Range), y**	**Total**	**Localized**[4]	**Advanced**[5]	**Advanced (restricted)**[6]	**Protate Cancer Mortality**[7]	**Low grade**[8]	**High grade**[9]
ATBC	Finland	1985-2002 (14)	26,963	49-70 (57)	1315	828	353	242	269	824	223
CARET	USA	1985-2005 (12)	10,402	44-75 (57)	730	439	68	**[10]	**[10]	551	79
CLUE II	USA	1989-2009 (19)	5,918	18-89 (51)	461	250	54	**[10]	**[10]	296	133
CPS II	USA	1992-2005 (12)	65,021	42-93 (64)	6863	5722	451	276	279	5375	1221
COSM	Sweden	1998-2008 (11)	43,010	45-79 (59)	2834	1774	513	381	293	1670	343
EPIC	10 European countries	1991-2006 (9)	142,174	20-97 (52)	2727	1337	345	175	248	1325	298
HPFS	USA	1986-2008 (21)	46,648	32-79 (54)	5410	3798	651	313	518	4008	556
JPHC I	Japan	1990-2008 (15)	20,016	40-59 (50)	135	78	**[10]	**[10]	**[10]	90	**[10]
JPHC II	Japan	1993-2004 (12)	23,780	40-69 (54)	162	82	**[10]	**[10]	**[10]	90	**[10]
MCCS	Australia	1990-2006 (13)	14,811	27-72 (55)	910	737	76	**[10]	70	668	218
MEC	USA	1993-2004 (11)	83,591	45-78 (60)	5525	4549	508	365	280	3632	1553
NLCS	Netherlands	1986-2007 [2] (13)	58,279	54-70 (61)	2359	1231	733	544	450	1686	490
NIH-AARP	USA	1995-2007 (10)	244,857	50-71 (62)	18497	13654	870	532	542	13463	3878
PCPT	USA	1994-2003 (7)	15,462	55-86 (63)	846	786	**[10]	**[10]	**[10]	678	107
PLCO	USA	1993-2008 (9)	29,840	55-75 (62)	2960	2543	140	87	78	2552	390
Total			830772		51734	36291	4762	2915	3027	36908	9489

[1]ATBC= Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, CARET=Beta-Carotene and Retinol Efficacy Trial , CLUE II=CLUE II: Campaign Against Cancer and Heart Disease, CPS II=Cancer Prevention Study II Nutrition Cohort, COSM=Cohort of Swedish Men, EPIC= European Prospective Investigation into Cancer and Nutrition, HPFS=Health Professionals Follow-up Study, JPHC I=The Japan Public Health Center-Based Study Cohort I, JPHC II=The Japan Public Health Center-Based Study Cohort II, MCCS=Melbourne Collaborative Cohort Study, MEC=Multiethnic Cohort, NLCS =Netherland Cohort Study, NIH-AARP=The NIH-AARP Diet and Health Study, PCPT=Prostate Cancer Prevention Trial, PLCO=Prostate, Lung, Colorectal, Ovarian Cancer Screening Trial

[2]Baseline cohort size and number of cases determined after applying exclusion criteria.

[3]NLCS is analyzed as a case-cohort study so the baseline cohort size does not reflect the exclusions, and we did not supply a median follow-up time for the cohort.

[4]"Localized": defined as cancers with information on stage but are not defined as "periprostatic", i.e. cancers confined within the prostate;

[5]"Advanced": defined as cancers with extension to or fixation to adjacent structures other than seminal vesicles, i.e. T4, N1, M1 or fatal;

[6]"Advanced (restricted)": same as "advanced" but excluding prostate cancer mortality cases that were initially diagnosed as localized cases or cases with missing stage information at diagnosis;

[7]"Prostate Cancer Mortality": defined when prostate cancer was the underlying cause of death

[8]"Low grade": Gleason score <8 or well/moderately differentiated;

[9]"High grade": Gleason score ≥8 or poorly differentiated/undifferentiated

[10]Studies with less than 50 cases were excluded from the analysis of that prostate cancer outcome and is denoted by **

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Table 2.

Median and Interquartile Range of Anthropometric Factors by Study

		Median (Interquartile Range)[2]						
Cohort[1]	**Age at BMI in Early Adulthood**	**BMI in Early Adulthood (kg/m^2)[3]**	**Age change[4]**	**BMI at baseline (kg/m^2)**	**BMI change[4]**	**Height (m)**	**Waist Circumference (cm)**	**Hip Circumference (cm)**
ATBC	**	**	**	26.0 (23.7-28.5)	**	1.74 (1.69-1.78)	**	**
CARET	**	**	**	27.7 (25.2-30.7)	**	1.75 (1.70-1.80)	**	**
CLUE II	21	22.7 (20.7-25.0)	30 (19-42)	25.9 (24.0-28.7)	3.3 (1.4-5.6)	1.78 (1.73-1.83)	**	**
CPS II	18	21.7 (19.8-23.7)	46 (41-50)	25.9 (24.0-28.4)	4.3 (2.2-6.6)	1.78 (1.75-1.83)	96.5 (91.4-104.1)	**
COSM	20	21.8 (20.4-23.3)	38 (31-47)	25.4 (23.6-27.7)	3.5 (1.7-5.6)	1.77 (1.73-1.82)	95.0 (90.0-102.0)	101.0 (97.0-106.0)
EPIC	20	22.6 (21.1-24.2)	34 (30-41)	26.1 (24.0-28.6)	3.3 (1.4-5.5)	1.75 (1.70-1.80)	94.2 (88.0-101.0)	101.0 (96.5-105.0)
HPFS	21	22.9 (21.1-24.4)	33 (24-41)	25.1 (23.5-27.1)	2.2 (0.8-4.1)	1.78 (1.73-1.83)	94.0 (88.9-100.3)	100.3 (96.5-104.8)
JPHC I	**	**	**	23.4 (21.6-25.3)	**	1.64 (1.60-1.68)	**	**
JPHC II	20	21.7 (20.3-23.3)	32 (25-40)	23.4 (21.5-25.3)	1.7 (−0.4-3.7)	1.64 (1.60-1.68)	**	**
MCCS	18-21	22.4 (20.8-24.2)	36 (28-43)	26.8 (24.7-29.0)	4.1 (2.0-6.5)	1.73 (1.68-1.78)	92.5 (86.7-99.0)	100.5 (96.5-105.0)
MEC	21	21.8 (20.2-23.8)	39 (31-46)	25.9 (23.9-28.8)	4.1 (2.1-6.5)	1.73 (1.68-1.78)	**	**
NLCS	20	21.7 (20.3-23.2)	42 (38-45)	24.8 (23.4-26.5)	3.1 (1.5-4.9)	1.76 (1.72-1.81)	**	**
NIH-AARP	18	21.4 (19.6-23.5)	45 (40-48)	26.6 (24.4-29.3)	5.0 (2.7-7.7)	1.78 (1.73-1.83)	96.5 (90.2-104.1)	101.6 (96.5-108.0)
PCPT	**	**	**	27.2 (25.0-29.8)	**	1.78 (1.73-1.83)	102.0 (95.3-109.0)	104.0 (99.0-109.0)
PLCO	20	22.8 (20.9-24.4)	44 (40-49)	27.0 (24.8-29.7)	4.2 (2.2-6.7)	1.78 (1.73-1.83)	**	**

[1]ATBC= Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, CARET=Beta-Carotene and Retinol Efficacy Trial , CLUE II=CLUE II: Campaign Against Cancer and Heart Disease, CPS II=Cancer Prevention Study II Nutrition Cohort, COSM=Cohort of Swedish Men, EPIC= European Prospective Investigation into Cancer and Nutrition, HPFS=Health Professionals Follow-up Study, JPHC I=The Japan Public Health Center-Based Study Cohort I, JPHC II=The Japan Public Health Center-Based Study Cohort II, MCCS=Melbourne Collaborative Cohort Study, MEC=Multiethnic Cohort, NLCS=Netherland Cohort Study, NIH-AARP=The NIH-AARP Diet and Health Study, PCPT=Prostate Cancer Prevention Trial, PLCO=Prostate, Lung, Colorectal, Ovarian Cancer Screening Trial

[2]Specific anthropometric factor was not assessed at baseline within this study and is denoted by **

[3]BMI at early adulthood was typically ascertained at baseline via self-report

[4]Age change represents the median age difference between age at baseline and age at BMI in early adulthood, which accounts for the age difference for the BMI change analysis (BMI at baseline - BMI in early adulthood).

Table 3.

Pooled Multivariable[1] Hazard Ratios (HR) and 95% Confidence Intervals (CI) of Prostate Cancer According to Body Mass Index at Baseline and in Early Adulthood

Anthropometric Factor	**HR (95% CI) by Categories of Anthropometric Factor**							***p-value*, test for trend[2]**	***p-value*, test for between-studies heterogeneity[3]**	**I^2 [4]**	***p-value*, test for common effects[5]**	**Continuous HR (95% CI) for 5kg/m^2 increment**	***p-value*, test for between-studies heterogeneity**	**I^2**
BMI in Early Adulthood (kg/m^2)	**<18.5**	**18.5-20.9**	**21.0-22.9**	**23.0-24.9**	**>25.0**									
All case N	**3266**	**11423**	**11049**	**7594**	**5159**									
Prostate Cancer mortality case N	**176**	**720**	**616**	**441**	**287**									
All	0.97 (0.93-1.01)	1.00 (0.97-1.03)	1.00 (REF)	0.98 (0.95-1.01)	0.94 (0.90-0.98)			0.33	0.18	30%		**[11]		
By stage														
Localized[6]	0.97 (0.92-1.01)	1.01 (0.97-1.05)	1.00 (REF)	0.98 (0.95-1.01)	0.91 (0.88-0.95)			<0.01	0.42	2%		**[11]		
Advanced[7]	0.86 (0.69-1.09)	0.95 (0.87-1.04)	1.00 (REF)	0.92 (0.77-1.11)	0.97 (0.85-1.10)			0.58	0.30	16%	0.42	1.01 (0.89-1.15)	<0.01	72%
Restricted[8]	0.98 (0.76-1.26)	0.95 (0.85-1.07)	1.00 (REF)	0.89 (0.70-1.13)	0.93 (0.79-1.08)			0.82	0.50	0%	0.89	0.97 (0.85-1.12)	0.01	62%
Prostate Cancer Mortality[9]	0.90 (0.66-1.24)	0.93 (0.83-1.03)	1.00 (REF)	0.95 (0.80-1.13)	0.99 (0.86-1.14)			0.43	0.52	0%	0.28	1.03 (0.89-1.20)	<0.01	69%
By grade														
Low[9]	0.95 (0.91-1.00)	1.01 (0.97-1.04)	1.00 (REF)	0.97 (0.93-1.01)	0.93 (0.87-0.99)			0.15	0.05	48%		**[11]		
High[10]	0.98 (0.89-1.07)	0.94 (0.87-1.01)	1.00 (REF)	0.98 (0.89-1.09)	0.95 (0.88-1.03)			>0.99	0.56	0%	0.61	1.00 (0.96-1.05)	0.89	0%
BMI at baseline (kg/m^2)		**<21.0**	**21.0-22.9**	**23.0-24.9**	**25.0-29.9**	**30.0-34.9**	**≥35.0**							
All case N		**1817**	**5546**	**11518**	**25407**	**6176**	**1270**							
Prostate Cancer mortality case N		**133**	**369**	**687**	**1426**	**338**	**74**							
All		0.96 (0.90-1.02)	1.00 (REF)	1.02 (0.99-1.06)	1.00 (0.96-1.05)	0.94 (0.89-1.00)	0.90 (0.81-1.00)	0.07	0.10	39%		**[11]		

Anthropometric Factor	**HR (95% CI) by Categories of Anthropometric Factor**						***p-value*, test for trend[2]**	***p-value*, test for between-studies heterogeneity[3]**	**I^2 [4]**	***p-value*, test for common effects[5]**	**Continuous HR (95% CI) for 5kg/m^2 increment**	***p-value*, test for between-studies heterogeneity**	**I^2**
By stage													
Localized[6]	0.97 (0.91-1.03)	1.00 (REF)	1.02 (0.97-1.07)	0.99 (0.95-1.04)	0.92 (0.88-0.96)	0.84 (0.76-0.93)	<0.01	0.25	23%		**[12]		
Advanced[7]	0.88 (0.74-1.04)	1.00 (REF)	0.97 (0.87-1.08)	1.01 (0.92-1.12)	1.05 (0.90-1.23)	1.30 (0.95-1.78)	0.01	0.11	37%	0.01	1.07 (1.02-1.12)	0.32	13%
Restricted[8]	0.74 (0.59-0.92)	1.00 (REF)	0.92 (0.81-1.04)	0.95 (0.83-1.09)	0.89 (0.75-1.05)	0.92 (0.68-1.25)	0.86	0.567	0%	0.60	1.01 (0.96-1.08)	0.34	11%
Prostate Cancer Mortality[9]	0.97 (0.79-1.19)	1.00 (REF)	0.96 (0.83-1.12)	1.02 (0.88-1.18)	1.13 (0.93-1.39)	1.52 (1.12-2.07)	<0.01	0.34	12%	<0.001	1.10 (1.05-1.16)	0.45	0%
By grade													
Low[10]	0.98 (0.92-1.05)	1.00 (REF)	1.01 (0.98-1.05)	0.99 (0.94-1.04)	0.91 (0.85-0.96)	0.81 (0.72-0.91)	<0.01	0.12	39%		**[12]		
High[11]	0.98 (0.86-1.11)	1.00 (REF)	1.06 (0.98-1.15)	1.03 (0.96-1.11)	1.03 (0.94-1.12)	1.15 (0.95-1.40)	0.18	0.23	27%	<0.01	1.03 (0.99-1.06)	0.30	18%
BMI change		**<25kg/m^2 in early adulthood, <30kg/m^2 at baseline**	**≥25kg/m^2 in early adulthood, <30kg/m^2 at baseline**	**<25kg/m^2 in early adulthood, ≥30kg/m^2 at baseline**	**≥25kg/m^2 in early adulthood, ≥30kg/m^2 at baseline**								
All case N		**30024**	**3281**	**3308**	**1878**								
Prostate Cancer mortality case N		**1760**	**189**	**188**	**98**								
All		1.00 (REF)	0.96 (0.92-1.01)	0.94 (0.91-0.97)	0.90 (0.83-0.97)			0.05	49%				
By stage													
Localized[6]		1.00 (REF)	0.95 (0.91-0.99)	0.93 (0.88-0.99)	0.85 (0.77-0.93)			0.03	54%				
Advanced[7]		1.00 (REF)	1.00 (0.88-1.14)	1.09 (0.96-1.24)	1.13 (0.93-1.38)			0.25	22%	0.01			
Restricted[8]		1.00 (REF)	0.96 (0.81-1.14)	0.98 (0.83-1.17)	1.02 (0.81-1.28)			0.54	0%	0.15			
Prostate Cancer Mortality[9]		1.00 (REF)	1.05 (0.90-1.23)	1.27 (1.09-1.49)	1.20 (0.95-1.52)			0.32	14%	0.01			

Anthropometric Factor	HR (95% CI) by Categories of Anthropometric Factor					*p-value*, test for trend[2]	*p-value*, test for between-studies heterogeneity[3]	I^2 [4]	*p-value*, test for common effects[5]	Continuous HR (95% CI) for 5kg/m^2 increment	*p-value*, test for between-studies heterogeneity	I^2
By grade												
Low[10]		1.00 (REF)	0.96 (0.91-1.02)	0.91 (0.87-0.95)	0.87 (0.79-0.95)		0.03	54%				
High[11]		1.00 (REF)	1.00 (0.91-1.09)	1.04 (0.94-1.16)	0.97 (0.87-1.08)		0.92	0%	0.12			
Absolute BMI change (kg/m^2)	**Loss > 2**	**+/− 2**	**2-<5**	**5-<10**	**≥10**							
All case N	**936**	**8846**	**14177**	**12170**	**2362**							
Prostate Cancer Mortality N	**58**	**588**	**803**	**651**	**135**							
All	1.00 (0.90-1.11)	1.00 (REF)	1.03 (1.00-1.07)	0.99 (0.94-1.04)	0.95 (0.91-1.00)	0.22	0.93	0%				
By stage												
Localized[6]	0.94 (0.86-1.02)	1.00 (REF)	1.03 (0.99-1.08)	0.97 (0.91-1.03)	0.94 (0.89-0.99)	0.07	0.89	0%				
Advanced[7]	0.94 (0.74-1.18)	1.00 (REF)	0.97 (0.84-1.12)	1.02 (0.88-1.19)	1.20 (0.93-1.55)	0.36	0.04	50%	0.11			
Restricted[8]	0.96 (0.72-1.30)	1.00 (REF)	0.98 (0.84-1.15)	0.98 (0.85-1.12)	1.08 (0.77-1.52)	0.95	0.05	52%	0.46			
Prostate Cancer Mortality[9]	1.01 (0.77-1.34)	1.00 (REF)	0.93 (0.78-1.11)	1.01 (0.84-1.20)	1.31 (0.99-1.74)	0.38	0.10	42%	0.02			
By grade												
Low[10]	0.99 (0.87-1.14)	1.00 (REF)	1.04 (0.99-1.08)	0.97 (0.91-1.03)	0.92 (0.86-0.97)	0.04	0.99	0%				
High[11]	1.07 (0.91-1.25)	1.00 (REF)	1.01 (0.93-1.09)	1.03 (0.96-1.11)	1.04 (0.93-1.16)	0.37	0.41	4%	0.06			

[1]Multivariable relative risks (MVRR) were adjusted for race (Caucasian, African-American, Asian, Hispanic, other), education (<high school, high school, >high school), marital status (married, never married, widowed, divorced), alcohol (0,>0-<5, 5-<15, 15-<30 and ≥30g/day), smoking habits (never, past smoker and <15 pack years, past smoker and ≥15 pack years, current smoker and <40 pack years, and current smoker and ≥40 pack years), height (<1.70, 1.70–<1.75, 1.75–<1.80, 1.80–<1.85, >1.85m except for JPHC1 and JPHC2 in which the .05m category increments ranged from <1.60 to >1.75m), physical activity (low, medium, high), prostate cancer family history (no, yes), personal history of diabetes (no, yes), multiple vitamin use (no, yes), and dietary calcium (quintiles), dietary lycopene (quintiles), and total energy intake (kcal/d, continuous); for adjustment, these variables were entered directly into the multivariable model or, for studies with less than 200 cases, these variables were modeled using propensity scores.

[2]P-value, test for trend is evaluated using the wald test

[3] P-value, test for between-studies heterogeneity is based on the highest category

[4] I^2 value is based on the highest category

[5] P-value, test for common effects, is based on the highest category and compared the following: 1)advanced to localized, 2) advanced restricted to localized, 3) prostate cancer mortality to localized, and 4) high grade to low grade.

[6] "Localized": defined as cancers with information on stage but are not defined as "periprostatic", i.e. cancers confined within the prostate;

[7] "Advanced": defined as cancers with extension to or fixation to adjacent structures other than seminal vesicles, i.e. T4, N1, M1 or fatal;

[8] "Advanced (restricted)": same as "advanced" but excluding prostate cancer mortality cases that were initially diagnosed as localized cases or cases with missing stage information at diagnosis

[9] "Prostate Cancer Mortality": defined when prostate cancer was the underlying cause of death

[10] "Low grade": Gleason score <8 or well/moderately differentiated

[11] "High grade": Gleason score ≥8 or poorly differentiated/undifferentiated

[12] Continuous estimates were not calculated as the p-value, test for nonlinearity<0.05

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Table 4.

Pooled Multivariable Hazard Ratios[1] and 95% Confidence Intervals(CI) of Prostate Cancer According to Waist and Hip Circumference

	HR (95% CI) by Categories of Anthropometric Factor				*p-value*, test for trend[2]	*p-value*, test for between-studies heterogeneity[3]	I^2 [4]	*p-value*, test for common effects[5]	Continuous HR (95% CI)[6]	*p-value*, test for between-studies heterogeneity	I^2
Waist Circumference (cm)	**<90**	**90-<100**	**100-<110**	**≥110**							
All Case N	**6048**	**11181**	**6291**	**2514**							
Prostate Cancer Mortality N	**292**	**571**	**337**	**165**							
All	1.00 (REF)	1.01 (0.96-1.06)	0.99 (0.95-1.04)	0.95 (0.90-1.00)	<0.01	0.79	0%		**[13]		
By stage											
Localized[7]	1.00 (REF)	1.01 (0.95-1.07)	0.98 (0.94-1.03)	0.93 (0.88-0.99)	<0.01	0.94	0%		**[13]		
Advanced[8]	1.00 (REF)	1.00 (0.89-1.13)	1.07 (0.94-1.22)	1.17 (0.95-1.44)	0.09	0.23	29%	0.04	1.05 (0.99-1.12)	0.12	44%
Restricted[9]	1.00 (REF)	0.94 (0.80-1.09)	1.03 (0.86-1.22)	0.92 (0.73-1.18)	0.98	0.65	0%	0.93	0.99 (0.93-1.05)	0.44	0%
Prostate Cancer Mortality[10]	1.00 (REF)	1.03 (0.89-1.19)	1.06 (0.90-1.25)	1.39 (1.14-1.71)	0.01	0.74	0%	<0.001	1.07 (1.01-1.13)	0.25	28%
By grade											
Low[11]	1.00 (REF)	1.00 (0.95-1.06)	0.97 (0.92-1.01)	0.90 (0.85-0.95)	<0.001	0.93	0%		**[13]		
High[12]	1.00 (REF)	1.06 (0.98-1.15)	1.11 (0.98-1.26)	1.16 (1.03-1.31)	0.02	0.40	5%	<0.001	1.05 (1.01-1.09)	0.20	34%
Hip Circumference (cm)	**<95**	**95-<100**	**100-<105**	**≥105**							
All Case N	**3017**	**4815**	**5517**	**6067**							
Prostate Cancer Mortality N	**158**	**265**	**333**	**391**							
All	1.00 (REF)	0.99 (0.94-1.05)	1.02 (0.96-1.09)	0.93 (0.87-0.98)	<0.01	0.28	25%		**[13]		
By stage											
Localized[7]	1.00 (REF)	1.00 (0.95-1.06)	1.02 (0.96-1.08)	0.92 (0.87-0.97)	<0.01	0.54	0%		**[13]		
Advanced[8]	1.00 (REF)	1.05 (0.84-1.32)	1.10 (0.85-1.43)	1.06 (0.83-1.36)	0.76	0.11	49%	0.26	1.02 (0.97-1.07)	0.06	57%

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	HR (95% CI) by Categories of Anthropometric Factor				*p-value*, test for trend[2]	*p-value*, test for between-studies heterogeneity[3]	I^2 [4]	*p-value*, test for common effects[5]	Continuous HR (95% CI)[6]	*p-value*, test for between-studies heterogeneity	I^2
Restricted[9]	1.00 (REF)	0.95 (0.72-1.27)	1.01 (0.74-1.38)	0.79 (0.63-0.98)	0.03	0.65	0%	0.18	0.98 (0.93-1.03)	0.55	0%
Prostate Cancer Mortality[10]	1.00 (REF)	1.03 (0.82-1.29)	1.20 (0.82-1.77)	1.26 (0.98-1.62)	0.03	0.24	29%	0.02	1.03 (0.98-1.07)	0.61	0%
By grade											
Low[11]	1.00 (REF)	1.00 (0.94-1.06)	1.00 (0.95-1.06)	0.88 (0.82-0.95)	<0.01	0.27	26%				
High[12]	1.00 (REF)	1.00 (0.89-1.12)	1.17 (0.93-1.48)	1.14 (0.92-1.41)	0.21	0.07	61%	0.03	1.01 (0.98-1.04)	0.30	25%
Waist to Hip Ratio	**<0.90**	**0.90-<0.95**	**0.95-<1.00**	**≥1.00**							
All Case N	**3792**	**6530**	**4820**	**3466**							
Prostate Cancer Mortality N	**207**	**385**	**283**	**228**							
All	1.00 (REF)	1.02 (0.98-1.07)	1.02 (0.97-1.06)	1.04 (0.99-1.09)	0.21	0.88	0%		1.01 (1.00-1.02)	0.72	0%
By stage											
Localized[7]	1.00 (REF)	1.01 (0.95-1.08)	1.03 (0.97-1.08)	1.03 (0.97-1.09)	0.47	0.66	0%		1.01 (0.99-1.02)	0.77	0%
Advanced[8]	1.00 (REF)	1.04 (0.91-1.20)	1.04 (0.86-1.27)	1.17 (0.95-1.45)	0.06	0.21	34%	0.24	**[13]		
Restricted[9]	1.00 (REF)	1.03 (0.76-1.38)	0.96 (0.78-1.18)	1.07 (0.79-1.46)	0.85	0.14	45%	0.80	1.01 (0.95-1.08)	0.52	0%
Prostate Cancer Mortality[10]	1.00 (REF)	1.02 (0.85-1.23)	1.01 (0.77-1.33)	1.20 (0.99-1.46)	0.07	0.61	0%	0.14	**[13]		
By grade											
Low[11]	1.00 (REF)	1.01 (0.95-1.07)	1.01 (0.96-1.07)	1.02 (0.96-1.08)	0.48	0.46	0%		1.00 (0.99-1.02)	0.37	9%
High[12]	1.00 (REF)	1.09 (0.95-1.25)	1.09 (0.98-1.22)	1.14 (1.01-1.28)	0.02	0.54	0%	0.09	1.05 (1.01-1.08)	0.53	0%

[1]Multivariable relative risks (MVRR) were adjusted for race (Caucasian, African-American, Asian, Hispanic, other), education (<high school, high school, >high school), marital status (married, never married, widowed, divorced), alcohol (0 ,>0-<5, 5-<15, 15-<30 and ≥30g/day), smoking habits (never, past smoker and <15 pack years, past smoker and 15+ pack years, current smoker and <40 pack years, and current smoker and pack years ≥40), height (<1.70, 1.70–<1.75, 1.75–<1.80, 1.80–<1.85, ≥1.85m), except for JPHC1 and JPHC2 in which the .05m category increments ranged from <1.60 to >1.75m, (physical activity (low, medium, high), prostate cancer family history (no, yes), personal history of diabetes (no, yes) multiple vitamin use (no, yes), and dietary calcium (quintiles), dietary lycopene (quintiles), and total energy intake (kcal/d, continuous); for adjustment, these variables were entered directly into the multivariable model or, for studies with less than 200 cases, these variables were modeled using the propensity scores.

[2] P-value, test for trend is evaluated using the Wald test

[3] P-value, test for between-studies heterogeneity is based on the highest category

[4] I^2 value is based on the highest category

[5] P-value, contrast test, is based on the highest category and compared the following: 1)advanced to localized, 2) advanced restricted to localized, 3) prostate cancer mortality to localized, and 4) high grade to low grade.

[6] Continuous estimate was based on an increment of 10cm for waist circumference, 5cm for hip circumference and 0.05 for waist to hip ratio.

[7] "Localized": defined as cancers with information on stage but are not defined as "periprostatic", i.e. cancers confined within the prostate;

[8] "Advanced": defined as cancers with extension to or fixation to adjacent structures other than seminal vesicles, i.e. T4, N1, M1 or fatal;

[9] "Advanced (restricted)": same as "advanced" but excluding prostate cancer mortality cases that were initially diagnosed as localized cases or cases with missing stage information at diagnosis

[10] "Prostate Cancer Mortality": defined when prostate cancer was the underlying cause of death

[11] "Low grade": Gleason score <8 or well/moderately differentiated

[12] "High grade": Gleason score >=8 or poorly differentiated/undifferentiated

[13] Continuous estimates were not calculated as the p-value, test for nonlinearity<0.05

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Table 5.

Pooled Multivariable Relative Risks (95% Confidence Intervals) of Prostate Cancer According to Height

Anthropometric Factor	**HR (95% CI) by Categories of Anthropometric Factor**							***p-value*, test for trend**[2]	***p-value*, test for between-studies heterogeneity**[3]	**I^2** [4]	***p-value*, contrast test**[5]	**Continuous HR (95% CI)**[6]	***p-value*, test for between-studies heterogeneity**	**I^2**
Height (m)	**<1.65**	**1.65-<1.70**	**1.70-1.75**	**1.75-1.80**	**1.80-1.85**	**1.85-1.90**	**>1.90**							
All Case N	**2088**	**4854**	**10609**	**14267**	**12520**	**5354**	**2042**							
Prostate Cancer Mortality N	**130**	**315**	**673**	**916**	**696**	**285**	**108**							
All	1.03 (0.97-1.09)	1.00 (REF)	1.02 (0.98-1.06)	1.03 (0.99-1.06)	1.04 (1.00-1.08)	1.02 (0.98-1.07)	1.09 (1.01-1.17)	0.12	0.22	26%		1.01 (1.00-1.01)	0.91	0%
By stage														
Localized[7]	1.06 (1.00-1.13)	1.00 (REF)	1.03 (0.98-1.08)	1.01 (0.97-1.06)	1.03 (0.99-1.08)	1.00 (0.95-1.05)	1.07 (0.97-1.18)	0.65	0.13	37%		1.00 (0.99-1.01)	0.82	0%
Advanced[8]	0.95 (0.79-1.13)	1.00 (REF)	1.07 (0.96-1.19)	1.15 (1.03-1.29)	1.17 (1.04-1.32)	1.17 (1.02-1.36)	1.33 (1.03-1.72)	<0.01	0.20	29%	0.13	1.05 (1.02-1.08)	0.24	22%
Restricted[9]	0.95 (0.75-1.21)	1.00 (REF)	1.10 (0.96-1.27)	1.12 (0.95-1.31)	1.18 (1.02-1.38)	1.11 (0.93-1.34)	1.33 (0.99-1.79)	<0.01	0.27	22%	0.19	1.04 (1.02-1.07)	0.72	0%
Prostate Cancer Mortality[10]	1.05 (0.81-1.36)	1.00 (REF)	1.08 (0.93-1.27)	1.25 (1.09-1.44)	1.25 (1.07-1.45)	1.29 (1.07-1.54)	1.56 (1.08-2.26)	<0.01	0.07	49%	0.05	1.07 (1.04-1.10)	0.25	22%
By grade														
Low[11]	1.08 (1.01-1.15)	1.00 (REF)	1.03 (0.99-1.08)	1.02 (0.98-1.07)	1.04 (0.99-1.08)	1.00 (0.95-1.06)	1.06 (0.99-1.13)	0.67	0.59	0%		**[13]		
High[12]	0.97 (0.86-1.09)	1.00 (REF)	1.00 (0.92-1.08)	1.05 (0.97-1.15)	1.09 (0.97-1.24)	1.10 (1.00-1.22)	1.02 (0.90-1.17)	0.01	0.76	0%	0.63	1.02 (1.00-1.04)	0.33	14%

[1] Multivariable relative risks (MVRR) were adjusted for race (Caucasian, African-American, Asian, Hispanic, other), education (<high school, high school, >high school), marital status (married, never married, widowed, divorced), alcohol (0 ,>0-<5, 5-<15, 15-<30 and ≥30g/day), smoking habits (never, past smoker and <15 pack years, past smoker and 15+ pack years, current smoker and <40 pack years, and current smoker and pack years ≥40), BMI (<23, 23-<25, 25-<30, >30kg/m^2), (physical activity (low, medium, high), prostate cancer family history (no, yes), personal history of diabetes (no, yes) multiple vitamin use (no, yes), and dietary calcium (quintiles), dietary lycopene (quintiles), and total energy intake (kcal/d, continuous); for adjustment, these variables were entered directly into the multivariable model or, for studies with less than 200 cases, these variables were modeled using the propensity scores.

[2] P-value, test for trend is based on the highest category

[3] P-value, test for between-studies heterogeneity is based on the highest category

[4] I^2 value is based on the highest category

[5] P-value, contrast test, is based on the highest category and compared the following: 1)advanced to localized, 2) advanced restricted to localized, 3) prostate cancer mortality to localized, and 4) high grade to low grade.

[6] Continuous estimate was based on an increment of 5cm for height.

[7] "Localized": defined as cancers with information on stage but are not defined as "periprostatic", i.e. cancers confined within the prostate;

[8] "Advanced": defined as cancers with extension to or fixation to adjacent structures other than seminal vesicles, i.e. T4, N1, M1 or fatal;

[9] "Advanced (restricted)": same as "advanced" but excluding prostate cancer mortality cases that were initially diagnosed as localized cases or cases with missing stage information at diagnosis

[10] "Prostate Cancer Mortality": defined when prostate cancer was the underlying cause of death

[11] "Low grade": Gleason score <8 or well/moderately differentiated

[12] "High grade": Gleason score >=8 or poorly differentiated/undifferentiated

[13] Continuous estimates were not calculated as the p-value, test for nonlinearity<0.05