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Height, obesity, and the risk of *TMPRSS2:ERG*-defined prostate cancer

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Abstract

Background—The largest molecular subtype of primary prostate cancer is defined by the *TMPRSS2:ERG* gene fusion. Few studies, however, have investigated etiologic differences by *TMPRSS2:ERG* status. Because the fusion is hormone-regulated and a man's hormonal milieu varies by height and obesity status, we hypothesized that both may be differentially associated with risk of *TMPRSS2:ERG*-defined disease.

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Methods—Our study included 49,372 men from the prospective Health Professionals Follow-up Study. Participants reported height and weight at baseline in 1986 and updated weight biennially thereafter through 2009. Tumor ERG protein expression (a *TMPRSS2:ERG* marker) was immunohistochemically assessed. We used multivariable competing risks models to calculate hazard ratios (HR) and 95% confidence intervals (CI) for the risk of ERG-positive and ERG-negative prostate cancer.

Results—During 23 years of follow-up, we identified 5,847 incident prostate cancers, among which 913 were ERG-assayed. Taller height was associated with an increased risk of ERG-positive disease only (per 5 inches HR: 1.24, 95% CI: 1.03–1.50, *P*-heterogeneity: 0.07). Higher BMI at baseline (per 5 kg/m^2 HR: 0.75, 95% CI: 0.61–0.91, *P*-heterogeneity: 0.02) and updated BMI over time (per 5 kg/m^2 HR: 0.86, 95% CI: 0.74–1.00, *P*-heterogeneity: 0.07) were associated with a reduced risk of ERG-positive disease only.

Conclusions—Our results indicate that anthropometrics may be uniquely associated with *TMPRSS2:ERG*-positive prostate cancer; taller height may be associated with greater risk, while obesity may be associated with lower risk.

Impact—Our study provides strong rationale for further investigations of other prostate cancer risk factors that may be distinctly associated with subtypes.

Keywords

TMPRSS2:ERG; prostate cancer; height; obesity; epidemiology

INTRODUCTION

The largest molecular subtype of primary prostate cancer is defined by the presence of gene fusions involving the transcription factor *ERG* (1). When the oncogene *ERG* binds to its most common fusion partner *TMPRSS2*, a gene regulated by androgens, the oncogene becomes androgen regulated as well (2). The fusion is unlikely prognostic by itself (3), but compelling evidence suggests it may play a role in prostate cancer progression, modifying the effect of obesity (4) and signaling pathways (5). There also exists preliminary evidence of risk factors associated with *TMPRSS2:ERG*-defined disease (6–10), though few etiologic studies have been conducted. Given that the search for prostate cancer risk factors has yielded few consistent associations and that the disease is heterogeneous, it follows that the search for risk factors for molecular subtypes could prove more fruitful. The identification of such risk factors could be critical toward developing personalized prevention strategies.

Anthropometrics are among the risk factors that could be differentially associated with *TMPRSS2:ERG*-defined disease. Obesity is characterized by reduced testosterone signaling, and tall height has been associated with increased androgen levels (11,12). Cell line experiments suggest that androgen exposure results in localization of *TMPRSS2* and *ERG*, thereby favoring fusion formation (13–17). Insulin-like growth factor (IGF) signaling influences height (18), appears enhanced in fusion-positive disease, and may promote fusion formation (4,19). One case-control study evaluated obesity with respect to *TMPRSS2:ERG*-defined disease (9). The investigators found that obesity is associated with a lower risk of fusion-positive prostate cancer, and they did not examine height (9).

We assessed the role of anthropometrics in the development of *TMPRSS2:ERG*-defined prostate cancer in the Health Professionals Follow-up Study (HPFS). We leveraged long-term anthropometric data to evaluate the hypotheses that height is *positively* associated with the risk of *TMPRSS2:ERG*-positive prostate cancer, and that body mass index (BMI) and waist circumference are *inversely* associated with risk.

MATERIALS AND METHODS

Study Population

The HPFS is an ongoing cohort of 51,529 male health professionals age 40 to 75 at enrollment in 1986. Participants responded to a baseline questionnaire concerning lifestyle and medical history, and have since completed follow-up questionnaires biennially. Follow-up for the surveys has been >90%. For this study, we excluded men with cancers other than nonmelanoma skin cancer at baseline (n=2,088) and who were missing baseline values for height or weight (n=35) or date of birth (n=34). The remaining 49,372 men free from prostate cancer at study initiation comprised our study population.

The Institutional Review Board at the Harvard T.H. Chan School of Public Health approved this study. Written informed consent was obtained from each subject.

Assessment of Anthropometric Measures

Participants reported height, weight at age 21, and weight at baseline, and weight biennially thereafter. Waist circumference was assessed in 1987. Self-reported weight and waist circumference were previously validated against technician-measured values with Pearson correlations of 0.97 and 0.95 respectively (20). Self-reported weight at age 21 has not been validated in the HPFS, but recalled weight during early adulthood in men has been shown to be accurate in other studies (21–23). Baseline BMI was calculated as reported weight in 1986 divided by the square of height reported in 1986 (kg/m^2). Updated BMI was calculated as weight reported on each follow-up questionnaire after 1986, divided by the square of height in reported in 1986 (kg/m^2; i.e., it was updated every two years in analyses). If data were missing after baseline for analyses of updated BMI over the course of follow-up, then data from previous questionnaire cycles were used. All three BMI exposures were significantly correlated (P-value < 0.001).

Ascertainment of Prostate Cancer Clinical Data

Prostate cancer cases were initially identified by self-report or participants' next-of-kin, and confirmed by medical record and pathology report. Given the accuracy of reporting among men with available medical records, these analyses included the 10 percent of cases indicated only by self-report or death certificates. Deaths were ascertained via reports from family members and inspection of the National Death Index. Follow-up for mortality was over 98 percent complete.

Study investigators reviewed records to abstract information about clinical stage, Gleason score and prostate-specific antigen (PSA) levels at diagnosis. To reduce detection bias, we

censored men diagnosed with stage T1a cancers (n=268) (24). In total, 5,847 prostate cancer cases were diagnosed during the study period.

Tumor Tissue Cohort and Immunohistochemistry

We retrieved archival formalin-fixed paraffin-embedded prostate tumor tissue from men who underwent radical prostatectomy (RP; 95%) or transurethral resection of the prostate (TURP; 5%). Tissue was unavailable from some hospitals and for men who were not treated with surgery. For this study, ERG data were available for 913 of the RP cases (and none of the TURP cases). Hematoxylin and eosin slides were reviewed by study pathologists to confirm cancer and identify tumor areas for tissue microarray (TMA) construction. We constructed TMAs by sampling at least three 0.6mm cores of tumor per case from the dominant nodule or nodule with highest Gleason (25). We used immunohistochemistry of ERG protein expression to characterize *TMPRSS2:ERG* status (Supplementary Figure S1), which has high concordance with alternative methods (26,27). Details of the assessment have been described previously (3). Briefly, ERG antisera (1:100, Clone ID: EPR3864, Epitomics, Inc., Burlingame, CA) were applied to 0.5-μm TMA sections and visualization of ERG was accomplished using the DAB substrate kit (Vector Laboratories Inc., Burlingame, CA). A case was scored ERG-positive if at least one TMA core had positive ERG staining within prostate cancer epithelial cells. Of cases positive for ERG in at least one core, 85% stained positive for ERG in all cores.

Statistical Analysis

We considered height, age 21 BMI, baseline BMI, updated BMI over the course of follow-up, and waist circumference in 1987 as both continuous (in five-unit increments) and categorical exposures. We reduced outlier influence on continuous exposures by employing a 99% Winsorization technique (28).

Person-time was calculated from return of the baseline questionnaire until prostate cancer diagnosis, death from any cause, or end of follow-up. Tumor tissue was characterized for ERG in cases diagnosed through February 2009; we thus ended follow-up at that time. For models investigating waist circumference, person-time accrual began in 1988. We used Cox proportional hazards models adjusted for age and calendar time to assess associations between anthropometric exposures and the risk of prostate cancer diagnosis. Because height and age 21 BMI cannot be affected by factors measured later in adulthood, their multivariable models only adjusted for age, calendar time, race, and family history of prostate cancer in a father or brother. Models for height were also adjusted for age 21 BMI and vice versa. Multivariable models of the remaining exposures were adjusted for the covariates in the table footnotes. For models of updated BMI, covariates besides height, age 21 BMI, race, and family history of prostate cancer were updated in each questionnaire cycle. For analyses of categorical exposures, we conducted linear trend tests across categories by modeling their median values continuously.

Next, we implemented an extension of Cox modeling as described by Lunn and McNeil that allows for exposure associations to vary by disease subtype (29,30). The details of this competing risks method have been described (7). These models allowed for estimating

hazard ratios separately for the risk of diagnosis with ERG-positive cancer and ERG-negative cancer versus no cancer. We tested heterogeneity across hazard ratios using likelihood ratio tests (31).

For overall and subtype-specific models of prostate cancer, we performed secondary analyses that applied inverse probability weights accounting for the unique clinical characteristics of cases assayed for ERG status. The methods to create these weights have been described (7). We explored confounding by PSA screening by stratifying by time period, examining associations separately for the pre-PSA (1986–1993) and PSA era (1994–2009).

Analyses were conducted using SAS version 9.4 (SAS Institute, Inc.; Cary, NC). Tests were two-sided with $P<0.05$ considered statistically significant.

RESULTS

Table 1 displays age-standardized characteristics of the study population by extreme categories of exposures at baseline (or in 1987 for waist circumference). Younger men tended to be taller, to have higher age 21 BMI, and a smaller waist circumference. Men in the lowest categories of BMI and waist circumference were most likely to be physically active, never have smoked, and use multivitamins.

During 23 years of follow-up, we identified 5,847 prostate cancer cases out of our cohort of 49,372 men (Table 2). Among the 2,402 men who were treated with RP, 913 (15.6% of all cases) were ERG-assayed and 439 (48.1% of assayed cases) were ERG-positive. Men treated with RP without tissue available were more likely diagnosed in later years. Lifestyle and demographic factors were otherwise similar for surgically-treated men with and without available tissue. Relative to surgically treated men, cases treated non-surgically were more likely older at diagnosis and to be diagnosed with higher grade, stage, and PSA levels. They also had a higher prevalence of diabetes and were less likely to have data regarding their clinical characteristics.

Table 3 presents multivariable results for anthropometric measures and risk of prostate cancer diagnosis overall and by ERG status; results from age- and calendar time-adjusted models were largely comparable (Supplementary Table S1). Increasing age 21 BMI was associated with a reduced risk of prostate cancer overall in both continuous (per 5 kg/m^2 HR: 0.92, 95% CI: 0.87–0.96) and categorical (≥25 kg/m^2 vs. <21 kg/m^2 HR: 0.89, 95% CI: 0.82–0.97, *P*-trend: 0.001) models. Baseline BMI also showed suggestive evidence of an inverse association with prostate cancer risk in continuous models only (per 5 kg/m^2 HR: 0.94, 95% CI: 0.89–1.00). Findings were largely similar when restricted to ERG-assayed cases. No other exposure was associated with prostate cancer overall.

Taller height was associated with an increased risk of diagnosis with ERG-positive prostate cancer (per 5 inches HR: 1.24, 95% CI: 1.03–1.50, Table 3), but not ERG-negative disease (*P*-heterogeneity: 0.07). Men with higher BMI at baseline (per 5 kg/m^2 HR: 0.75, 95% CI: 0.61–0.91, *P*-heterogeneity: 0.02) and over time (per 5 kg/m^2 HR: 0.86, 95% CI: 0.74–1.00, *P*-heterogeneity: 0.07) had a reduced risk of ERG-positive disease only. Higher age 21 BMI

(per 5 inches HR: 0.87, 95% CI: 0.73–1.03) and waist circumference (per 5 kg/m^2 HR: 0.85, 95% CI: 0.72–1.02) showed suggestive associations with a reduced risk of ERG-positive disease only, but heterogeneity tests across subtypes were nonsignificant.

Applying inverse probability weights did not materially change the results (Supplementary Table S2). Analyses stratified by PSA era were not well-powered to detect associations or heterogeneity, but results were qualitatively similar (Supplementary Table S3).

DISCUSSION

As the molecular taxonomy of prostate cancer has become clearer (1) it has become imperative to investigate disease etiology by prostate cancer subtype. Using an integrative molecular epidemiology approach, we found that taller height was associated with a higher risk of ERG-positive prostate cancer, and that baseline and updated obesity were associated with a lower risk. Evidence was only suggestive that age 21 BMI and waist circumference were associated with ERG-positive prostate cancer only; neither test of heterogeneity was significant. In sum, our results indicate that height and obesity are uniquely associated with the risk of ERG-positive prostate cancer. They also provide strong rationale for further investigations of other prostate cancer risk factors that may be distinctly associated with subtypes.

Androgen signaling likely promotes *TMPRSS2:ERG* (6,13–17,32,33). Exposing prostate cancer cells (13–15,33) and immortalized nonmalignant cells (16) to dihydrotestosterone appears to promote the fusion. In the HPFS and Physicians' Health Study, we found that increasing circulating free testosterone may be associated with a higher risk of ERG-positive disease only (6). Some (16,32), but not all (34,35) investigations, have reported that shorter polymorphic CAG repeat sequence in exon 1 of *androgen receptor* (*AR*) is associated with risk of ERG-positive disease only. The polymorphic CAG repeat is inversely associated with transcriptional activity of *AR* (36). As testosterone levels tend toward inverse correlations with obesity and potentially positive correlations with height (11,12), these variations in testosterone signaling offer a plausible explanation for our findings.

This is the first investigation of the association between height and ERG-defined prostate cancer. Height has been shown to be modestly associated with an increased risk of total prostate cancer (37). We found no association, as is consistent with previous findings in the HPFS of positive associations with advanced and lethal prostate cancer only (38). Taller men may experience greater testosterone exposure over the life-course (12,39,40), and a pooled analysis found a weak positive association between serum testosterone and height (12). It follows that testosterone signaling may link height and *TMPRSS2:ERG*.

The IGF signaling pathway may also operate in the association between height and fusion-positive prostate cancer. IGF signaling is important in determining height (18), and evidence suggests that the IGF pathway is upregulated in fusion-positive cancers. Our group found higher IGF1 receptor (IGF1R) expression in ERG-positive tumors than in ERG-negative tumors (4). Another study found IGF1R was more highly expressed in the *ERG*-positive VCaP prostate cancer cell line than in cell lines lacking *ERG*, and transfecting *ERG* into

other malignant cell lines increased IGF1R expression (19). Knockdown of *ERG* in VCaP cells also reduced IGF1R expression (19). Collectively, these data suggest greater IGF signaling in fusion-positive cancer. To the best of our knowledge, however, the role of IGF signaling in promoting *TMPRSS2:ERG* is untested.

Obesity has been consistently inversely associated with the risk of less aggressive prostate cancer (41). Regarding *TMPRSS2:ERG*-defined prostate cancer, our findings align with the only previous study to investigate obesity as a risk factor (9). It too found that obesity was distinctly associated with fusion-positive disease, reporting a 14% reduction in the odds of ERG-positive prostate cancer for every 5 kg/m^2 increase in BMI (9). Obesity is characterized by lower circulating testosterone levels (11). Consistent with experimental research, our findings may be explained by lower circulating testosterone levels in obese men that reduce the risk for developing *TMPRSS2:ERG*. That the rate of obesity is higher (42,43) and the rate of the fusion is lower (44–46) in populations of African ancestry relative to Caucasians lends additional support to our findings. It should be noted, however, that populations of East Asian ancestry also have lower rates of the fusion (3,45–47), but tend toward lower rates of obesity (42,43). While detection bias due to hemodilution and greater biopsy sampling error in obese men may also partly explain an inverse association between obesity and prostate cancer (48), it is unlikely these issues would differ according to *TMPRSS2:ERG* status. We previously found obesity to be associated with a greater risk of lethal prostate cancer among men with fusion-positive tumors (4). It could be that the low testosterone environment of obesity is associated with reduced development of fusion-positive tumors, but following development of fusion-positive disease, increased growth stimulating hormone levels promote lethal progression. Further study is required to clarify these mechanisms and address the role of obesity in the development of *TMPRSS2:ERG*-positive prostate cancer in individuals of non-Caucasian ancestry.

While age 21 BMI and waist circumference were suggestively associated with a reduced risk of ERG-positive prostate cancer, tests of heterogeneity across subtypes were nonsignificant. The only other study to evaluate recalled BMI in early adulthood and *TMPRSS2:ERG*-defined disease found similarly nonsignificant but suggestive results (9). The distribution of age 21 BMI in our cohort could have been too limited to observe a clear difference in associations with ERG-defined disease. Regarding waist circumference, no prior study has investigated associations with ERG-defined disease. Our results suggest that waist circumference may not be differentially associated with ERG-defined disease and/or that we were limited in our ability to evaluate the exposure; we had only one measurement during mid- to late-adulthood.

Strengths of our study include leveraging a large well-annotated prospectively-monitored cohort. We collected exposure data prior to diagnosis and adjusted for potentially important demographic and lifestyle confounders. However, our cohort was comprised primarily of white men, limiting generalizability to other racial/ethnic groups. We did not directly measure *TMPRSS2:ERG*, though IHC for ERG has excellent agreement with fluorescence in situ hybridization (26) and polymerase chain reaction (27). Finally, the cases for which we were able to assay ERG status, which were largely treated with RP, may not be representative of all men diagnosed with prostate cancer. However, their characteristics were

not substantially different from other prostate cancer cases, and sensitivity analyses applying inverse probability weights did not appreciably change results.

In summary, we found that height was positively associated with risk of ERG-positive prostate cancer and that obesity, particularly later in life, was inversely associated with ERG-positive disease. Our results may reflect differences in exposure to androgens and/or IGF1 by height and obesity status. These findings suggest that prostate cancer etiology differs according to *TMPRSS2:ERG* status, and support conducting similar investigations beyond anthropometrics. Moreover, further studies are needed to validate our findings and clarify the mechanisms by which obesity and height may be linked with the development of *TMPRSS2:ERG*-positive prostate cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AR	androgen receptor
BMI	body mass index
CI	confidence interval
HPFS	Health Professionals Follow-up Study
HR	hazard ratio
IGF	insulin-like growth factor
IGF1R	insulin-like growth factor 1 receptor
PSA	prostate-specific antigen

RP	radical prostatectomy
TMA	tissue microarray
TURP	transurethral resection of the prostate

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Table 1

Age-adjusted characteristics of the Health Professionals Follow-up Study at baseline in 1986 (unless otherwise noted) according to extreme categories of anthropometric exposures

	Height		BMI at Age 21		BMI		Waist Circumference, 1987[a]	
Characteristic	**≤68 in**	**>72 in**	**<21 kg/m^2**	**≥25 kg/m^2**	**<23 kg/m^2**	**≥27.5 kg/m^2**	**≤35 inches**	**≥40 inches**
Number	13,196	8449	10,804	10,703	8752	10,190	8895	7424
Mean Height, in (SD)	66.9 (1.4)	74.0 (1.1)	70.3 (2.5)	70.1 (2.7)	70.2 (2.6)	70.1 (2.8)	69.2 (2.5)	71.0 (2.6)
Mean BMI at Age 21, kg/m^2 (SD)	23.1 (2.8)	23.0 (2.9)	19.6 (1.0)	26.9 (2.0)	21.0 (2.0)	25.3 (3.1)	21.9 (2.2)	24.3 (3.2)
Mean BMI, kg/m^2 (SD)	25.7 (3.3)	25.5 (3.2)	23.6 (2.5)	28.2 (3.5)	21.7 (1.0)	30.1 (2.6)	22.9 (1.8)	28.9 (3.1)
Mean Waist Circumference, 1987, in (SD)	36.3 (3.4)	38.8 (3.6)	36.1 (3.2)	39.6 (3.9)	34.1 (2.2)	41.8 (3.3)	33.5 (1.3)	42.4 (2.4)
Mean Age, years (SD)[b]	56.5 (10.2)	52.2 (9.0)	56.7 (10.0)	52.9 (9.2)	54.0 (10.3)	54.7 (9.2)	54.0 (9.7)	58.4 (9.5)
Caucasian	11,509 (91.6%)	7800 (97.0%)	9699 (93.9%)	9798 (96.6%)	7825 (94.1%)	9292 (96.0%)	7976 (93.9%)	6877 (97.1%)
Family History of Prostate Cancer	1508 (11.4%)	1042 (12.2%)	1289 (12.0%)	1193 (11.1%)	1034 (11.9%)	1169 (11.4%)	1183 (13.4%)	1004 (13.4%)
Diabetes	509 (3.4%)	240 (3.3%)	370 (2.9%)	431 (4.4%)	237 (2.7%)	475 (4.6%)	209 (2.8%)	453 (5.5%)
Top Quintile of Physical Activity (≥28.5 METS / week)	1853 (15.1%)	1363 (15.0%)	1213 (12.2%)	1719 (15.2%)	1878 (21.3%)	815 (8.1%)	2277 (24.1%)	604 (8.6%)
Smoking Status								
Never	5972 (48.3%)	3807 (45.2%)	4622 (46.0%)	4697 (45.1%)	4407 (51.7%)	4146 (42.7%)	4631 (52.1%)	2879 (41.5%)
Past, Quit >10 Years Before Baseline	3995 (29.9%)	2309 (30.7%)	3440 (31.0%)	2991 (30.4%)	2317 (28.0%)	3077 (31.2%)	2394 (29.9%)	2382 (31.3%)
Past, Quit ≤10 Years Before Baseline	1515 (12.2%)	1156 (13.9%)	1322 (12.8%)	1488 (14.1%)	790 (9.3%)	1574 (16.0%)	846 (9.6%)	1218 (17.3%)
Current	1188 (9.6%)	839 (10.2%)	1049 (10.2%)	1083 (10.5%)	915 (11.0%)	989 (10.1%)	723 (8.5%)	685 (9.9%)
Multivitamin Use	5521 (42.2%)	3508 (43.0%)	4629 (42.8%)	4263 (40.9%)	4071 (47.6%)	4688 (36.8%)	4093 (47.3%)	2933 (39.6%)
Had Screening PSA Test, 1994[c]	4604 (36.7%)	2864 (38.5%)	3795 (36.8%)	3589 (37.5%)	3031 (38.9%)	3343 (35.1%)	3264 (41.9%)	2897 (40.8%)
Had Screening PSA Test, 2004[c]	5402 (58.3%)	4070 (62.3%)	4406 (59.2%)	4896 (60.9%)	4039 (62.0%)	4181 (57.8%)	4803 (67.6%)	3269 (66.1%)
Mean Nutrient & Food Intakes								
Total Calories, kcal/day (SD)	1922 (603)	2061 (630)	1999 (610)	1964 (622)	2005 (600)	1997 (637)	2003 (597)	2022 (631)
Lycopene, µg/day (SD)	7505 (4956)	7068 (4610)	7068 (4767)	7617 (4899)	6939 (4659)	7563 (4936)	6973 (4602)	7307 (4826)
Calcium, mg/day (SD)	875 (398)	918 (413)	861 (391)	907 (409)	911 (413)	883 (398)	925 (411)	893 (406)
Alpha-linolenic Acid, g/day (SD)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)	1.0 (0.3)	1.1 (0.3)	1.0 (0.3)	1.1 (0.3)
Supplemental Vitamin E, mg/day (SD)	37.4 (83.9)	39.0 (84.6)	35.6 (80.4)	38.4 (86.4)	44.1 (89.3)	33.6 (81.9)	43.4 (88.0)	33.6 (80.6)
Alcohol, g/day (SD)	10.1 (14.1)	12.0 (15.4)	11.4 (15.2)	10.5 (14.4)	10.6 (14.1)	10.8 (15.2)	10.8 (14.0)	11.6 (15.9)

	Height		BMI at Age 21		BMI		Waist Circumference, 1987[a]	
Characteristic	**≤68 in**	**>72 in**	**<21 kg/m^2**	**≥25 kg/m^2**	**<23 kg/m^2**	**≥27.5 kg/m^2**	**≤35 inches**	**≥40 inches**
Coffee, cups/day (SD)	1.9 (1.7)	1.9 (1.8)	1.7 (1.7)	2.1 (1.8)	1.7 (1.7)	2.1 (1.8)	1.7 (1.7)	2.1 (1.8)

Note: Numbers may not add up to total sample sizes for characteristics with missing data; percentages may not add up as expected due to rounding

Abbreviations: BMI: body mass index; in: inches; METS: metabolic equivalents; PSA: prostate-specific antigen; SD: standard deviation

[a] Waist circumference reported in 1987; all other characteristics (with the exception of PSA screening history) reported for 1988 rather than 1986

[b] Not adjusted for age

[c] Reported having a PSA test in the two years prior to the questionnaire date

Table 2

Characteristics of participants with prostate cancer in the Health Professionals Follow-up Study at the time of diagnosis (unless otherwise noted), by treatment and ERG status

	Participants Treated with Radical Prostatectomy		Participants Treated Otherwise	
Characteristic	**ERG-positive**	**ERG-negative**	**ERG Status Unavailable**	**ERG Status Unavailable**
Number	439	474	1489	3445
Year of Diagnosis				
1986–1990	35 (8.0%)	28 (5.9%)	122 (8.2%)	295 (8.6%)
1991–1995	157 (35.8%)	151 (31.9%)	396 (26.6%)	781 (22.7%)
1996–2000	134 (30.5%)	151 (31.9%)	356 (23.9%)	896 (26.0%)
2000–2005	74 (16.9%)	99 (20.9%)	342 (23.0%)	932 (27.1%)
2006–2009	39 (8.9%)	45 (9.5%)	273 (18.3%)	541 (15.7%)
Mean Age, years (SD)	65.1 (6.0)	65.8 (5.7)	65.9 (5.9)	72.9 (6.9)
Mean PSA Level, ng/mL (SD)[a]	9.7 (11.5)	10.2 (12.4)	11.5 (109)	20.7 (151)
% Missing	32 (7.3%)	41 (8.6%)	141 (9.5%)	913 (26.5%)
Biopsy Gleason Score				
2–6[a]	265 (66.9%)	265 (63.1%)	821 (66.3%)	1482 (56.9%)
7[a]	107 (27.0%)	112 (26.7%)	338 (27.3%)	731 (28.1%)
8–10[a]	24 (6.1%)	43 (10.2%)	80 (6.5%)	392 (15.1%)
% Missing	43 (9.8%)	54 (11.4%)	250 (16.8%)	840 (24.4%)
Clinical Stage				
T1 / T2[a]	416 (94.8%)	453 (95.6%)	1392 (95.5%)	2473 (87.5%)
T3[a]	19 (4.3%)	14 (3.0%)	41 (2.8%)	112 (4.0%)
T4 / N1 / M1[a]	4 (0.9%)	7 (1.5%)	24 (1.7%)	243 (8.6%)
% Missing	0 (0.0%)	0 (0.0%)	32 (2.2%)	617 (17.9%)
Mean Height, inches (SD)	70.5 (2.6)	70.2 (2.7)	70.2 (2.5)	69.9 (2.6)
Mean BMI at Age 21, kg/m^2 in (SD)	22.8 (2.6)	23.0 (2.6)	22.8 (2.6)	22.7 (2.7)
Mean BMI, kg/m^2 (SD)	25.7 (3.1)	26.1 (3.2)	25.7 (3.1)	25.9 (3.5)
Mean Waist Circumference in 1987, inches (SD)	36.9 (3.1)	37.5 (3.3)	36.9 (3.4)	37.7 (3.4)
Caucasian	409 (97.6%)	433 (96.2%)	1381 (97.1%)	3137 (95.4%)
Family History of Prostate Cancer	94 (21.4%)	116 (24.5%)	346 (23.2%)	625 (18.1%)
Diabetes	21 (4.8%)	21 (4.4%)	70 (4.7%)	315 (9.1%)
Top Quintile of Physical Activity (≥28.5 METS/week)	59 (13.4%)	68 (14.4%)	260 (17.5%)	440 (12.8%)
Smoking Status[a]				
Never	215 (50.8%)	231 (50.9%)	687 (47.7%)	1474 (44.1%)
Past, Quit >10 Years Before Diagnosis	135 (31.9%)	154 (33.9%)	531 (36.9%)	1296 (38.8%)
Past, Quit ≤10 Years Before Diagnosis	48 (11.4%)	41 (9.0%)	159 (11.0%)	395 (11.8%)

Characteristic	Participants Treated with Radical Prostatectomy		Participants Treated Otherwise	
	ERG-positive	ERG-negative	ERG Status Unavailable	ERG Status Unavailable
Current	25 (5.9%)	28 (6.2%)	63 (4.4%)	175 (5.2%)
Multivitamin Use	227 (51.7%)	253 (53.6%)	829 (55.9%)	2003 (58.4%)
Had Screening PSA Test	203 (46.2%)	231 (48.7%)	751 (50.4%)	1742 (50.6%)
Mean Nutrient & Food Intakes				
Total Calories, kcal/day (SD)	1966 (528)	1976 (522)	1930 (535)	1965 (545)
Lycopene Intake, μg/day (SD)	6898 (3937)	7091 (3774)	7328 (4075)	7116 (4206)
Calcium, mg/day (SD)	945 (370)	922 (348)	945 (366)	967 (374)
Alpha-linolenic Acid, g/day (SD)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)
Supplemental Vitamin E, mg/day (SD)	51.1 (79.2)	55.4 (80.1)	59.7 (85.1)	64.4 (86.6)
Alcohol, g/day (SD)	12.0 (13.3)	12.3 (14.6)	10.5 (12.0)	12.0 (14.5)
Coffee, cups/day (SD)	1.9 (1.6)	1.9 (1.6)	1.9 (1.5)	1.8 (1.5)

Note: Numbers may not add up to total sample sizes for characteristics with missing data; percentages may not add up as expected due to rounding

Abbreviations: BMI: body mass index; in: inches; METS: metabolic equivalents; PSA: prostate-specific antigen; SD: standard deviation

[a] Among those with data available

Table 3

Multivariable hazard ratios (HR) and 95% confidence intervals (CI) for association between anthropometric exposures and risk of prostate cancer, both overall and by ERG status, Health Professionals Follow-up Study, 1986–2009

	All Cases		Radical Prostatectomy Cases Assayed for ERG Status Only				
	# Cases	Overall HR (95% CI)	# ERG+ Cases	# ERG− Cases	Overall HR (95% CI)	ERG-Positive HR (95% CI)	ERG-Negative HR (95% CI)
Height[a]							
Continuous, per 5 inches	5847	1.03 (0.98–1.08)	439	474	1.10 (0.97–1.26)	1.24 (1.03–1.50)	0.98 (0.82–1.18)
P-heterogeneity						0.07	
Categorical, inches							
≤68	1594	1.00 (ref)	88	133	1.00 (ref)	1.00 (ref)	1.00 (ref)
>68 – 70	1780	1.06 (0.99–1.13)	138	128	1.05 (0.87–1.25)	1.39 (1.06–1.82)	0.82 (0.64–1.05)
>70 – 72	1531	1.00 (0.93–1.08)	127	119	1.01 (0.84–1.21)	1.32 (1.00–1.75)	0.80 (0.62–1.02)
>72	942	1.05 (0.96–1.14)	86	94	1.19 (0.97–1.45)	1.42 (1.05–1.93)	1.03 (0.79–1.35)
P-trend		0.51			0.21	0.02	0.71
P-heterogeneity						0.02	
BMI at Age 21[b]							
Continuous, per 5 kg/m^2	5591	0.92 (0.87–0.96)	419	461	0.91 (0.81–1.03)	0.87 (0.73–1.03)	0.96 (0.81–1.12)
P-heterogeneity						0.43	
Categorical, kg/m^2							
<21	1427	1.00 (ref)	109	105	1.00 (ref)	1.00 (ref)	1.00 (ref)
21 – <23	1663	0.99 (0.93–1.07)	125	118	0.88 (0.73–1.06)	0.89 (0.69–1.15)	0.87 (0.67–1.13)
23 – <25	1400	0.93 (0.86–1.00)	103	143	0.95 (0.79–1.15)	0.80 (0.61–1.05)	1.11 (0.86–1.43)
≥25	1101	0.89 (0.82–0.97)	82	95	0.80 (0.65–0.98)	0.73 (0.55–0.98)	0.87 (0.66–1.15)
P-trend		0.001			0.07	0.03	0.69
P-heterogeneity						0.20	
BMI at Baseline in 1986[c]							
Continuous, per 5 kg/m^2	5715	0.94 (0.89–1.00)	428	466	0.87 (0.76–1.00)	0.75 (0.61–0.91)	0.99 (0.84–1.18)
P-heterogeneity						0.02	
Categorical, kg/m^2							

	All Cases		Radical Prostatectomy Cases Assayed for ERG Status Only				
	# Cases	Overall HR (95% CI)	# ERG+ Cases	# ERG− Cases	Overall HR (95% CI)	ERG-Positive HR (95% CI)	ERG-Negative HR (95% CI)
<23	1038	1.00 (ref)	94	72	1.00 (ref)	1.00 (ref)	1.00 (ref)
23 – <25	1698	1.04 (0.96–1.14)	140	133	1.04 (0.84–1.28)	0.96 (0.73–1.28)	1.13 (0.83–1.54)
25 – <27.5	1860	0.97 (0.89–1.05)	122	167	0.93 (0.75–1.16)	0.72 (0.53–0.97)	1.20 (0.89–1.62)
≥27.5	1119	0.97 (0.88–1.08)	72	94	0.88 (0.67–1.15)	0.71 (0.50–1.02)	1.09 (0.76–1.55)
P-trend		0.29			0.22	0.02	0.72
P-heterogeneity						0.05	
Updated BMI[c]							
Continuous, per 5 kg/m^2	5838	0.99 (0.95–1.03)	439	474	0.95 (0.85–1.06)	0.86 (0.74–1.00)	1.03 (0.90–1.18)
P-heterogeneity						0.07	
Categorical, kg/m^2							
<23	975	1.00 (ref)	70	57	1.00 (ref)	1.00 (ref)	1.00 (ref)
23 – <25	1527	1.10 (1.01–1.20)	126	133	1.30 (1.04–1.63)	1.16 (0.86–1.57)	1.48 (1.07–2.04)
25 – <27.5	1799	1.04 (0.96–1.13)	136	144	1.10 (0.88–1.38)	1.02 (0.75–1.38)	1.20 (0.88–1.65)
≥27.5	1537	1.06 (0.97–1.16)	107	140	1.10 (0.87–1.41)	0.87 (0.63–1.21)	1.38 (0.99–1.92)
P-trend		0.68			0.79	0.14	0.31
P-heterogeneity						0.19	
Waist Circumference in 1987[cd]							
Continuous, per 5 inches	4058	0.98 (0.93–1.03)	333	347	0.96 (0.84–1.08)	0.85 (0.72–1.02)	1.06 (0.90–1.25)
P-heterogeneity						0.07	
Categorical, inches							
≤35	1079	1.00 (ref)	102	83	1.00 (ref)	1.00 (ref)	1.00 (ref)
>35 – 37	1080	1.02 (0.93–1.12)	96	92	1.13 (0.91–1.42)	1.12 (0.83–1.53)	1.15 (0.84–1.58)
>37 – <40	982	0.94 (0.85–1.04)	77	92	1.12 (0.89–1.41)	1.00 (0.72–1.38)	1.25 (0.91–1.72)
≥40	917	0.95 (0.85–1.05)	58	80	0.94 (0.73–1.22)	0.79 (0.55–1.13)	1.11 (0.78–1.57)
P-trend		0.13			0.52	0.12	0.59
P-heterogeneity						0.44	

Abbreviations: BMI: body mass index; CI: confidence interval; HR: hazard ratio

[a] Models adjusted for age, calendar time, race (Caucasian, African-American, Asian-American, other), family history of prostate cancer in father or brother (yes, no), and BMI at age 21 (<21, 21–<23, 23–<25, 25+ kg/m^2)

[b] Models adjusted for age, calendar time, race (Caucasian, African-American, Asian-American, other), family history of prostate cancer in father or brother (yes, no), and height (≤68, >68–70, >70–72, >72 inches)

[c] Models adjusted for age, calendar time, race (Caucasian, African-American, Asian-American, other), family history of prostate cancer in father or brother (yes, no), height (≤68, >68–70, >70–72, >72 inches), BMI at age 21 (<21, 21–<23, 23-<25, 25+ kg/m^2), vigorous physical activity (quintiles of metabolic equivalents-hours/week), smoking (never, former / quit >10 years ago, former / quit ≤10 years ago, current), diabetes (yes, no), prostate-specific antigen testing (yes, no lagged by one period to avoid counting diagnostic PSA tests as screening; models of updated BMI only), use of multivitamins (yes, no), total calories (continuous), and intakes of calcium, alpha-linolenic acid, lycopene, supplemental vitamin E, alcohol (quintiles) and coffee (none, <1, 1–<2, 2–<3, 3+ cups/day

[d] Follow-up starting in 1988