Body Size and Composition and Prostate Cancer Risk

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Abstract

Reported associations between body measurements and the risk of prostate cancer are weak and inconsistent, possibly because some measures used do not differentiate between adipose and nonadipose tissue, body components that would theoretically have different associations with prostate cancer. Some studies have addressed this problem by estimating lean body mass from subjects' age, height, and weight. In a prospective cohort study of men 27–75 years of age at recruitment in 1990–1994, body measurements were taken by trained interviewers. Nonadipose and adipose mass were calculated from bioelectric impedance analysis. Incident prostate cancers were ascertained by use of the population cancer registry. Altogether 16,336 men contributed 113,535 person-years and 477 cancers, of which 79 were "aggressive," to the analysis. We found no overall association between prostate cancer and any anthropometric measurement. Analysis stratified by cancer aggressiveness revealed modest associations between measures of adiposity and the risk of aggressive disease. On the basis of the WHO cut points and compared with men in the normal range of body mass index, the risk ratio for obese men was 2.2 (95% confidence interval, 1.2–4.1). For each 10-kg increase in fat mass, the risk ratio was 1.4 (95% confidence interval, 1.0–1.8). Energy imbalance may play a role in the development of aggressive prostate cancer.

Introduction

Body size and composition have long been hypothesized to influence the risk of prostate cancer. Scientific interest in anthropometric measurements and prostate cancer has included birth weight, body size attained at maturity around age 18–21 years, and adult body size and composition in later life. The evidence that any of these factors is associated with prostate cancer is weak and inconsistent (1). Explanations for the inconsistencies include problems with study design, statistical power, exposure assessment, limitations of body mass index (BMI), and lack of disease specificity related to the phenotypic heterogeneity of prostate cancer (2). Another plausible explanation is that there is little or no association between body size measures and prostate cancer risk.

Most studies of prostate cancer and anthropometry have relied on computations of BMI to measure obesity and leanness (3–11). Unfortunately, BMI is an imperfect measure of obesity that combines adipose and nonadipose body components, and does not take account of variation attributable to body frame size (12). Measurement of adipose and nonadipose mass by the current "gold standard" methods of dual-energy X-ray absorptiometry or hydrostatic weighing is costly and time consuming and difficult in frail, elderly subjects. A few studies have examined a possible relationship between prostate cancer and nonadipose mass [lean body mass (LBM)], using an algorithm based only on age, height, and weight, but findings have been inconclusive (13–16). Estimates of adipose and nonadipose mass can feasibly be obtained in large cohort studies using measures of resistance and reactance from bioelectric impedance analysis plus height and weight.

We assessed the relationship between estimates of body size and composition and risk of prostate cancer in a prospective cohort study by making direct anthropometric measurements, including bioelectric impedance analysis, which was used to estimate adipose and nonadipose mass.

Materials and Methods

The Cohort. The Melbourne Collaborative Cohort Study is a prospective cohort study of 41,528 people (17,049 men) 27–75 years of age at baseline, 41,247 (99.3%) of whom were 40–69 years of age (17). Recruitment occurred between 1990 and 1994. The study protocol was approved by the human research ethics committee of The Cancer Council Victoria. Southern European migrants to Australia (including 2419 Italian men and 2073 Greek men) were deliberately oversampled to extend the range of lifestyle exposures and to increase genetic variation.

Subjects were recruited through the Electoral Rolls (registration to vote is compulsory for adults in Australia), advertisements, and community announcements in local media (*e.g.*, television, radio, newspapers). Comprehensive lists of Italian and Greek surnames were also used to target southern European migrants in the phone book and Electoral Rolls.

Passive follow-up has been conducted by record linkage to Electoral Rolls, electronic phone books, and to the Victorian Cancer Registry and death records to June 30, 2002. Over the course of the study, 342 men have moved out of Victoria (2.0% of all men in the cohort) and 1247 (7.3%) have died.

Subjects. Of the 17,049 men recruited, 406 (2.4%) were excluded from analysis because they had a diagnosis of prostate cancer before baseline, had a cancer other than prostate cancer diagnosed in the 5 years before baseline, or had died or been

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diagnosed with any cancer within the first 30 days after baseline. An additional 79 men (0.5%) who did not have a complete set of valid anthropometric measurements were also excluded, leaving 16,564 men.

Measurements. Height, weight, and waist and hip circumferences were measured once at baseline attendance for each participant according to written protocols that were based on standard procedures (18). Weight was measured to 100 g by digital electronic scales, height to 1 mm by a stadiometer, and waist and hip circumferences to 1 mm by a metal anthropometric tape. Bioelectric impedance analysis was performed with a single-frequency (50 kHz) electric current produced by a BIA-101A RJL system analyzer (RJL Systems, Detroit, MI). Resistance and reactance were measured with subjects in a supine position. Heart rate was measured by Dinamap automatic monitors, which were programmed to take three consecutive readings of systolic pressure, diastolic pressure, and pulse rate at 3-min intervals in subjects relaxed in reclining seats for at least 5 min after fitting of blood pressure cuffs. At the interview, questions were asked on conventional demographics such as country of birth and highest level of education.

Identification of Incident Prostate Cancers. All subjects gave written consent allowing access to their medical records for confirmation of diagnoses. Cases were identified from notifications to the Victorian Cancer Registry of diagnoses of adenocarcinoma of the prostate (*International Classification of Diseases*, 9th revision, rubric 185, or 10th revision, rubric C61). Gleason score was ascertained and used to categorize prostate cancer grade into low (Gleason score 1–4), moderate (Gleason score 5–7), and high (Gleason score 8–10). High-grade prostate cancers and metastatic cases were grouped together as "aggressive" prostate cancer.

Statistical Analysis. Cox's proportional hazards regression models with age as the time axis (19) were used to estimate the rate ratios associated with each anthropometric measure, adjusting for country of birth (Australia, Greece, Italy, United Kingdom) and highest level of education (primary school, some high/technical school, completed high school, and completed tertiary degree/diploma). Results from analyses excluding the first 2 years of follow-up (men possibly with undetected prostate cancer at baseline) differed from results without this exclusion; therefore, our calculation of person-time commenced 2 years after baseline and ended at date of diagnosis of prostate cancer or date of censoring. Subjects were censored at the date of their deaths, the date they left Victoria, or June 30, 2002 (the date that ascertainment of prostate cases by the Victorian Cancer Registry was complete).

We estimated fat-free mass (FFM) as $9.1536 + (0.4273 \times \text{height}^2/\text{resistance}) + (0.1926 \times \text{weight}) + (0.0667 \times \text{reactance})$ (20). Fat mass (weight − FFM) and percentage of fat (fat mass divided by weight) were subsequently calculated. LBM was calculated using the algorithm $(2.447 - 0.09516 \times \text{age} + 0.1074 \times \text{height} + 0.3362 \times \text{weight})/0.732$ (21). BMI was calculated as weight in kg divided by the square of height in meters. Waist-to-hip ratio was also computed. The heart rate used for analysis was the mean of the second and third measures. Anthropometric measures were fitted as continuous covariates to estimate linear trends on the log hazard ratio scale. In the case of BMI, analysis was also performed using categories (<25, 25–29, and ≥ 30 kg/m^2), and fat mass was also analyzed in quartiles based on the distribution of the entire cohort.

Separate analyses were conducted excluding the Greek- and Italian-born men because of the strong associations between southern European country of birth and anthropometric measures. Polytomous logistic regression models, adjusting for age (as a quadratic), country of birth, and highest level of education were used to test the heterogeneity in the odds ratios between low-grade, moderate-grade, and aggressive prostate cancer (22). For each anthropometric measure, the odds ratios obtained from polytomous logistic regression were almost identical to the risk ratios (RRs) obtained from Cox's proportional hazard modeling (all within 0.03 of each other).

Statistical analyses were performed with STATA/SE 7.0 (Stata Corporation, College Station, TX). $P < 0.05$ (two-sided) was considered statistically significant. Tests based on Schoenfeld residuals and graphical methods using Kaplan–Meier curves (23) showed no evidence that proportional hazard assumptions were violated for any of the anthropometric measures.

Results

During 113,535 person-years of follow-up from 1992 to 2002, 477 prostate cancers (472 histopathologically confirmed and 5 metastatic) were identified from 16,336 men. Nearly 90% of the cases were men >60 years of age at the time of diagnosis, and the mean age of diagnosis was 67 years (range, 47–80 years). Mean values for height, weight, BMI, percentage of fat, and waist-to-hip ratio differed by age, country of birth, and education level (data not shown). Men with aggressive prostate cancer tended to be slightly shorter, had a greater percentage of fat and BMI, and larger waist and hip circumferences than noncases (Table 1).

Relationships between individual anthropometric measures and risks of prostate cancer by grade, adjusted for age, country of birth, and highest level of education, are presented in Table 2. Both hip circumference and percentage fat were positively related to overall prostate cancer incidence, with values of statistical significance tests nominally >0.05.

Height had a stronger negative association with aggressive disease, although the difference in RRs between grades was not statistically significant. A stronger association for aggressive disease with BMI was observed, but the test for homogeneity across grades was of borderline statistical significance ($P = 0.05$). All other anthropometric measures had stronger positive associations with aggressive disease, although none of the tests for homogeneity across grades was significant.

Assessment of aggressive prostate cancer alone showed that increased levels of all anthropometric measures, apart from height, were associated with increased risk. Many of these associations, including weight, waist and hip circumferences, fat mass, and BMI, were statistically significant (all $P < 0.05$).

To further illustrate these associations, we divided fat mass into quartiles and found that compared with the lowest quartile, the RR for men in the second quartile was 1.1 [95% confidence interval (95% CI), 0.6–2.2], whereas the RR for men in the third quartile was 1.3 (95% CI, 0.7–2.4), and finally the RR for men in the highest quartile was 1.6 (95% CI, 0.8–2.9). Using the WHO cut points and compared with men in the normal range of BMI, the RR for overweight men was 1.1 (95% CI, 0.6–1.9), whereas the RR for obese men was 2.2 (95% CI, 1.2–4.1).

Estimates of the risk of aggressive prostate cancer for increased levels of LBM were higher than those for FFM but still did not reach statistical significance (RR = 1.32/10-kg increase; 95% CI, 0.92–1.91). When all analyses were repeated excluding Greek- and Italian-born men, we obtained similar results (data not shown).

Table 1 Mean values (SD) for each anthropometric measurement for all cases (by grade)[a] and noncases

	All cases (n = 477)		Low grade (n = 66)		Moderate grade (n = 332)		Aggressive (n = 79)		Noncases (n = 15,859)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age at baseline (years)	61.2	6.0	61.8	5.9	60.6	6.1	63.2	5.2	54.9	8.8
Height (cm)	171.4	6.8	172.0	7.6	171.5	6.4	170.6	7.9	172.5	7.4
Weight (kg)	80.5	11.5	81.3	13.3	79.9	10.3	82.4	14.3	80.9	11.8
Waist circumference (cm)	94.9	10.3	95.2	12.8	94.3	9.5	97.0	11.0	93.5	10.0
Hip circumference (cm)	101.9	7.3	102.5	9.5	101.4	6.4	103.5	8.5	101.0	7.0
Fat-free mass (kg)	56.5	5.8	57.0	6.3	56.3	5.5	57.2	6.6	57.2	5.8
Fat mass (kg)	24.0	7.7	24.3	9.3	23.6	6.9	25.2	9.0	23.7	7.8
Percentage fat	29.2	5.8	29.1	6.7	29.1	5.5	29.8	6.0	28.7	6.0
Body mass index (kg/m^2)	27.4	3.6	27.5	4.2	27.2	3.4	28.3	4.0	27.2	3.6
Waist-to-hip ratio	0.93	0.06	0.93	0.08	0.93	0.06	0.94	0.06	0.92	0.06
Heart rate (beats/min)[b]	66.9	10.6	65.9	12.7	67.1	10.5	67.0	9.1	67.3	10.5

[a] Gleason score was ascertained and used to categorize prostate cancer grade into low (Gleason score 1–4), moderate (Gleason score 5–7), or high (Gleason score 8–10). High-grade prostate cancers and metastatic cases were grouped together as aggressive prostate cancer.
[b] On basis of 475 prostate cancers (66 low grade, 331 moderate grade, and 78 aggressive) and 15,813 noncases.

Discussion

We found no overall association between prostate cancer and any anthropometric measurement. Analysis stratified by cancer aggressiveness revealed modest associations between measures of adiposity and the risk of aggressive disease. Because of our marginal statistical power to detect differences between subgroups, this observation should be interpreted cautiously.

The associations that we have described are not large, and we have therefore considered whether such modest associations might be attributable to some form of bias or error. Generally, the prospective nature of the study and the high levels of follow-up achieved would have reduced many possible sources of bias. On the other hand, detection bias may have occurred because an unknown proportion of our cases would not have been detected had it not been for testing for prostate-specific antigen (PSA), which was widespread during follow-up (24, 25). To reduce the effect of possible bias attributable to screening, we adjusted for education and country of birth, both of which are likely to be determinants of testing for PSA (25), and which were related to our anthropometric measures. Given the strong association between anthropometric measures and country of birth, the analysis we performed that excluded Greek- and Italian-born men confirmed the associations with measures of adipose mass and thus diminished concern about residual confounding. More importantly, we observed the strongest relationships for the most aggressive prostate tumors, the incidence of which would not be as influenced by testing for PSA; for example, the European Randomized Study of Screening for Prostate Cancer trial showed that 8% of prostate cancers detected in the first round of screening and 3% of prostate cancers in the second round were of high grade, compared with 22% in the unscreened group (26).

With regard to the estimates of FFM and fat mass, we chose a formula that had been developed with Caucasian populations of similar age and BMI distribution to our own (20) and that had been validated by use of sound statistical techniques. Because the algorithm to compute FFM and fat mass includes height, weight, resistance, and reactance, in theory any measurement errors in these would have reduced the precision of FFM and fat mass estimates. In practice, however, these errors are generally small; therefore, the consequences for precision are likely to have been minimal. Finally, our use of standardized procedures and methods for the direct measurement of height and weight would have minimized nondifferential measurement errors that would have attenuated the strength of associations.

We consider that our findings are novel and credible. Anthropometric studies in relation to prostate cancer have been reviewed extensively by Nomura (2). Cohort studies included in that review showed little persuasive evidence of relationships

Table 2 Rate ratios[a] (95% confidence intervals in parentheses) of overall, low-grade, moderate-grade, and aggressive[b] prostate cancer risk in relation to anthropometric measurements

	All cases (n = 477)	Low grade (n = 66)	Moderate grade (n = 332)	Aggressive (n = 79)
Height (per 10 cm)	0.94 (0.81–1.08)	1.14 (0.78–1.67)	0.93 (0.78–1.10)	0.82 (0.58–1.15)
Weight (per 10 kg)	1.02 (0.95–1.11)	1.09 (0.89–1.34)	0.97 (0.88–1.07)	1.20 (1.00–1.44)
Waist circumference (per 10 cm)	1.06 (0.97–1.16)	1.09 (0.85–1.39)	1.00 (0.90–1.12)	1.29 (1.04–1.60)
Hip circumference (per 10 cm)	1.12 (0.99–1.27)	1.25 (0.90–1.73)	1.02 (0.88–1.19)	1.44 (1.09–1.90)
Fat-free mass (per 10 kg)	0.96 (0.82–1.13)	1.14 (0.75–1.73)	0.87 (0.71–1.05)	1.25 (0.85–1.83)
Fat mass (per 10 kg)	1.08 (0.96–1.22)	1.14 (0.83–1.56)	1.01 (0.88–1.17)	1.35 (1.03–1.77)
Percentage fat (per 10%)	1.16 (0.99–1.35)	1.10 (0.72–1.66)	1.12 (0.93–1.34)	1.39 (0.95–2.06)
Body mass index (per 5 kg/m^2)	1.09 (0.96–1.24)	1.10 (0.77–1.55)	1.00 (0.86–1.17)	1.51 (1.14–2.01)
Waist-to-hip ratio (per 0.1 units)	1.00 (0.86–1.16)	0.93 (0.62–1.38)	0.97 (0.82–1.16)	1.17 (0.82–1.68)
Heart rate (beats/min)[c]	1.00 (0.92–1.09)	0.92 (0.73–1.17)	1.02 (0.92–1.12)	1.03 (0.83–1.27)

[a] All rate ratios (per unit of change) are adjusted for age, country of birth, and highest level of education.
[b] Gleason score was ascertained and used to categorize prostate cancer grade into low (Gleason score 1–4), moderate (Gleason score 5–7), and high (Gleason score 8–10). High-grade prostate cancers and metastatic cases were grouped together as aggressive prostate cancer.
[c] On basis of 475 prostate cancers (66 low grade, 331 moderate grade, and 78 aggressive).

between prostate cancer and height. We, among others (9, 10, 13, 14, 16, 27, 28), have also failed to detect a relationship between prostate cancer incidence and height. A few studies have seen a positive relationship (6–8, 15, 29), which would be consistent with associations between insulin-like growth factor-1 and height (30) and insulin-like growth factor-1 and prostate cancer risk (31). Our finding of a moderately higher risk of aggressive prostate cancer associated with increased hip circumference contrasts to an inverse relationship found in the Health Professionals Follow-up Study (8), but this finding relied on self-measured hip circumferences.

With regard to other findings concerning nonadipose mass and prostate cancer, three previous cohort studies calculated LBM from measured height and weight (14–16). A study of Swedish construction workers found a weak association for prostate cancer incidence (RR = 1.2; 95% CI, 1.0–1.3) and mortality (RR = 1.3; 95% CI, 1.0–1.6) for the highest LBM categories (15). A second study of Norwegian men displayed no consistent relationship (RR = 1.1; 95% CI, 0.8–1.4; Ref. 14), whereas a third, smaller study of 154 cases reported a null relationship but gave no details (16). In another study, LBM was calculated from reported height and weight (13). The rate ratio in the highest category of LBM was 1.0 (CI, 0.7–1.3). In this instance, it is possible that a true association may have been attenuated because of misclassification (32, 33). We found no compelling evidence of a relationship between FFM or LBM and aggressive or overall prostate cancer incidence. In summary, the evidence to date supports, at most, a very weak effect of increased nonadipose mass on prostate cancer risk.

More than a dozen cohort studies have previously looked at a possible BMI–prostate cancer relationship (3–11, 13–16, 28, 34). The most noteworthy findings to date have been observed in regard to prostate cancer mortality (5, 11, 15), with little or no evidence for an effect on overall incidence. Only a few studies have examined "advanced" prostate cancer (6, 8, 10, 13), with some (8, 10) finding results similar (albeit not statistically significant) to the mortality studies. Our results suggest that men with an increased BMI, in particular those who are obese ($\geq$30 kg/m^2), may be at increased risk of more severe forms of prostate cancer. Any BMI effect, however, is probably related to an effect of adipose rather than nonadipose tissue. It has been speculated that obesity and increased fat mass relative to nonadipose tissue, which is associated with increased levels of circulating estrogens (35), could theoretically protect against prostate cancer (36). BMI and prostate cancer may possibly be associated through sympathetic nervous system activity (37), such as resting heart rate. Although some have reported that resting heart rate was associated with prostate cancer mortality (38) or incidence (39), other studies, including the present study, have not found an effect (40).

It has also been speculated that energy imbalance (a surplus of intake over expenditure) may increase prostate cancer risk (41), and in this regard, physical inactivity may play an important part. The effects we have reported for adipose tissue and BMI may simply reflect this imbalance. To date, however, studies investigating possible effects of physical activity or dietary energy intake on prostate cancer risk have reported at best weak and inconsistent findings (42, 43). Energy imbalance in males tends to increase central obesity, which has also been shown to be associated with male colon cancer (44). Central obesity can lead to hyperinsulinemia and alterations to the insulin-like growth factor-1 axis (45), and there is a growing literature supporting a role for insulin-like growth factor-1 in prostate carcinogenesis (46). Furthermore, a recent case-control study of (mainly nonobese) Chinese men found an association between insulin resistance and increased prostate cancer incidence (47). Central obesity may also alter leptin levels (48), but the evidence is inconsistent (49–51). Leptin has angiogenic activity (52) that correlates with metastasis (53). Any adiposity and prostate cancer association may thus be attributable to disease progression rather than incidence. This is consistent with our observations of adiposity associations solely in regard to aggressive disease.

Notwithstanding the many possible biological mechanisms involved, our finding that measures of adiposity are related to a modestly increased risk of aggressive prostate cancer supports the case for public health initiatives to combat the growing prevalence of obesity and physical inactivity in populations such as that of Australia.

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