Height, Body Weight, and Risk of Prostate Cancer

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Abstract

Using data from the Health Professionals Follow-Up Study, we prospectively examined the relationships between height, body mass index, waist and hip circumferences, and risk of total and advanced (extraprostatic and metastatic) prostate cancer. In addition, we assessed adiposity during childhood, adolescence, and early adulthood using pictograms in relation to prostate cancer risk. Between 1986 and 1994, 1,369 cases of prostate cancer (excluding stage A1) were confirmed in 47,781 men. Adult body mass index and waist and hip circumferences were not appreciably related to risk of total prostate cancer or advanced prostate cancer. In contrast, preadult (age 10) obesity assessed in 33,336 men in 1988 was prospectively related to lower risk of advanced [relative risk (RR) = 0.72 with 95% confidence interval (CI) = 0.47–1.10], between high and low quintiles; \( P_{\text{trend}} = 0.06 \) and metastatic prostate cancer (RR = 0.38 with 95% CI = 0.19–0.77; \( P_{\text{trend}} = 0.004 \)). For the advanced lesions, an association was observed with height (RR = 1.68 with 95% CI = 1.16–2.43 for men 74 inches or taller, relative to men 68 inches or shorter; \( P_{\text{trend}} = 0.01 \)). In an analysis limited to particularly aggressive forms of prostate cancer, i.e., cases found to be metastatic at time of diagnosis between 1988 and 1994 after a negative digital rectal examination in 1988, we found that obesity at ages 5 and 10 had a strong inverse association (RR = 0.16 with 95% CI = 0.05–0.54, between high and low quintiles at age 10) and that tallness had a strong direct association with risk of metastatic disease (RR = 2.29 with 95% CI = 1.04–5.05, for height ≥74 inches versus ≤68 inches). Our findings suggest that the preadult hormonal milieu, as reflected in attained height and childhood obesity, may have a strong influence on prostate carcinogenesis.

Introduction

In men, obesity is associated with various endocrine aberrations, including higher serum estrogen and lower testosterone levels (1–6). On the basis that this hormonal pattern may decrease risk of prostate cancer (7), a lower rate of this malignancy may be predicted among heavier men. On the other hand, increased body weight has been linked to higher risk of several malignancies. Studies of obesity in relation to prostate cancer risk have yielded inconsistent results. Case-control studies have not generally supported an association between BMI and risk of prostate cancer (8–14), but one study found a direct association (15). Prospective data on BMI and risk of prostate cancer have been conflicting, with some studies supporting a direct association (16, 17) and others finding no relationship (18, 19). BMI is correlated with both adiposity and lean body mass (20). The results from one prospective study (21) indicated that a direct association between BMI and risk of prostate cancer was due to lean body mass rather than adiposity, suggesting that BMI may not be an unconfounded measure of obesity in this circumstance.

The studies examining obesity and prostate cancer have focused on adult BMI. The prostate gland is essentially dormant until puberty, when hormonal changes stimulate its development. Recent studies demonstrating that prostatic intraepithelial neoplasia, a cancer precursor lesion, is already common among men in their twenties (22, 23) suggest that prostatic carcinogenesis begins early. The influence of hormones may be particularly strong during puberty and adolescence, when the prostate achieves full development. Attained height and preadult obesity may reflect events that occur during this period, characterized by profound changes in levels of sex hormones, growth hormone, and IGF-1. Taller individuals are at higher risk of several malignancies, including colon and breast cancer (24, 25), but the available data examining height as a risk factor for prostate cancer are conflicting; some studies support an association (26–28) whereas others do not (14, 19). Preadult adiposity has not been studied.

Using data from the Health Professionals Follow-Up Study, we examined the relationships between height, BMI, and risk of prostate cancer occurrence and progression. In addition, we examined the RR of prostate cancer associated with waist and hip circumferences, indicators of fat distribution, and measures of adiposity less confounded with lean body mass. We also used adiposity level during childhood, adolescence, and early adulthood to examine the relationship between body mass at the period of prostate development and prostate cancer risk.

Patients and Methods

Study Population. The Health Professionals Follow-Up Study is an ongoing prospective cohort study of the causes of cancer

1 The abbreviations used are: BMI, body mass index; IGF-1, insulin-like growth factor-I; RR, relative risk; PSA, prostatic specific antigen; CI, confidence interval.
and heart disease in men (29). The cohort consists of 51,529 American male dentists, optometrists, osteopaths, pharmacists, podiatrists, and veterinarians who were 40–75 years old and responded to a mailed questionnaire in 1986. We elicited information on age, marital status, height and weight, ancestry, medications, disease history, physical activity, and diet. The assessment of anthropometric measures (30), diet (31), and physical activity (32) have been validated in substudies within the cohort. To form the analytic cohort, we excluded 2218 men who reported cancer at baseline (other than nonmelanoma skin cancer). To be able to control for dietary factors, we also excluded 1,530 men who did not adequately complete the dietary questionnaire [they left 70 or more items blank or reported intake of more than 17,600 joules (4,200 kcal) or less than 3,350 joules (800 kcal) per day]. After these baseline exclusions, 47,781 participants remained.

Follow-Up of the Cohort. Follow-up questionnaires were sent in 1987, 1988, 1990, 1992, and 1994 to ascertain new cases of a variety of diseases and to update and expand exposure information. In 1994, the participant was asked whether he had received a PSA examination. Most of the deaths in the cohort were reported by family members or by the postal system in response to the follow-up questionnaires, which included certified mail to nonresponders. In addition, we searched the National Death Index, a highly sensitive method (33), to identify deaths among nonresponders. Because the age-adjusted incident rate of prostate cancer in our cohort was quite comparable to United States rates (actually 6% higher in our cohort), based on the Surveillance, Epidemiology, and End Results (SEER) Program data from 1986 to 1989 before widespread PSA screening, we are likely to have detected the vast majority of diagnosed prostate cancers in our cohort.

Assessment of Anthropometric Variables. Men reported their current weight, height, and weight at age 21 on the 1986 baseline questionnaire. In 1987, we mailed a supplementary questionnaire to all cohort members to obtain additional exposure information, including circumference measures, not included on the 1986 baseline questionnaire. We instructed the participant to measure (to the nearest quarter of an inch) his waist at the umbilicus and his hips at the largest circumference between the waist and thighs while standing and avoiding bulky clothing (30). Along with the questionnaire, we provided a tape measure and an illustration to standardize the measurements. We used BMI (kg/m²) as a measure of total adiposity, waist:hip ratio as a measure of relative distribution of fat, and waist circumference to estimate total abdominal fat (34). We also evaluated weight change during adulthood, assessed as weight in 1986 minus weight at age 21.

We evaluated the precision of self-reported anthropometric measures among a sample of the cohort members who were part of a dietary validation study (30). Briefly, trained technicians visited randomly selected Boston-area cohort members of similar age distribution as the entire cohort twice, approximately 6 months apart, to measure current weight and waist and hip circumferences. The Pearson correlation between self-report and the average of the technicians' two measurements was 0.97 for weight, 0.95 for waist circumference, 0.88 for hip circumference, and 0.69 for waist:hip ratio. Relative to the technicians' measurements, the men slightly overestimated their waist (0.36 in) and underestimated their hip circumference (0.78 in) and weight (2.3 pounds).

To estimate level of adiposity during different periods throughout life, we included a section on the 1988 questionnaire that depicted nine illustrations of body builds or figures ranging from thin to obese and asked the participant to select the figure that best described his body build at each of the following ages: 5, 10, 20, 30, 40, and current age (35). The remote recall of childhood weight and body build by elderly subjects using these pictograms has been previously shown in another population to provide useful information in ranking individuals (36). For example, in 71–76-year-old individuals, the correlations between their recalled preadult body build and direct measures of the BMI that had been taken at the corresponding time period were mostly in the range of 0.5–0.7 (36).

Identification of Cases of Prostate Cancer. On the 1988, 1990, 1992, and 1994 questionnaires, we inquired about a diagnosis of prostate cancer during the prior 2 years. Upon a report, we asked the man for written permission to obtain hospital records and pathology reports. For deceased men, we contacted next of kin. After repeated mailings, we received questionnaires or confirmed deaths of more than 96% of eligible participants in 1988 and in 1990, 94% in 1992, and 90% in 1994, thus accounting for 94% of the total possible person-years of follow-up. We estimate having ascertained over 98% of the deaths in this cohort. From 1986 to the end of this study period (January 31, 1994), we identified 1411 incident cases of prostate cancer. Of these, 1226 cases (87%) were confirmed by medical records, 150 (11%) additional men provided information regarding the basis of diagnosis and subsequent treatment, and 35 (2%) could not be recontacted. When we obtained medical records and pathology reports, a diagnosis of adenocarcinoma of the prostate was confirmed in 99% of the cases. Because of the high accuracy of reporting prostate cancer, we analyzed all men who reported a diagnosis of prostate cancer, even if we could not review medical records.

A study physician staged prostate cancers according to information received from medical reports [stage A, occult or incidental finding (A1, focal; A2, diffuse); stage B, confined to prostate gland; stage C, localized to periprostatic area; stage D1, metastatic disease involving only regional lymph nodes; and stage D2, those that have metastasized to other organs]. This classification criteria included information from any work-up during the initial diagnosis, including staging prostatectomy and bone scans. Prostatectomy could result in upstaging of apparent stage B cancers (tumors with penetration through the capsule move to stage C, and those with lymph node metastases move to stage D1). Because approximately 60% of the men received a prostatectomy, some advanced cancers may have been missed.

From 1986 to 1989, the age-specific incidence rates of prostate cancer were constant, and the vast majority of cases were initially detected via routine rectal examination, due to surgery for benign prostatic hyperplasia or due to symptoms. The age-specific incidence rate approximately doubled in the subsequent 4-year period (1990–1993), presumably because of wider use of serum PSA level for screening. By January 1994, almost 80% of men older than 60 years had received a PSA examination.

Data Analysis. Each of the participants was followed beginning on the month of return of the baseline questionnaire and ending on the month of diagnosis of prostate cancer, month of death from other causes, or the end of the study period. For exposures assessed initially in follow-up questionnaires (circumferences in 1987, and preadult pictograms in 1988), follow-up time accrued beginning on the month of return of these questionnaires. We calculated incidence rates of prostate cancer for men in a specific category (of body mass, height, etc.) by dividing the number of incident cases by the number of person-
years. The RR was computed as the rate among men in a specific category divided by the rate among men in a specified reference category. We used the Mantel-Haenszel summary estimator (37) to adjust for age (across 2.5-year categories), and multivariate logistic regression with repeated measures (38) biennially to estimate RRs when controlling simultaneously for more than one risk factor. We tested for linear trends using the Mantel-Haenszel extension test for trend in the age-adjusted analysis, was attenuated when we controlled additionally for height and BMI at age 21. The attenuation was noted: men who were 74 inches tall were at 60-70% greater risk of being diagnosed with the more advanced forms of the disease than were men who were ≤68 inches tall.

We examined waist and hip circumference measures assessed in 1987 in relation to prostate cancer risk. Among men who met inclusion criteria, 30,966 provided data on this in 1987. No appreciable association was noted for waist circumference, but an inverse association was noted between hip circumference and total, advanced, and metastatic prostate cancer (Table 4). The inverse association between hip circumference and risk of metastatic prostate cancers persisted when we controlled BMI at age 21; \( P_{\text{trend}} = 0.19 \). As for the overall analysis, the slight suggestion of an inverse association did not persist when we controlled BMI at age 21. Adult weight gain (weight in 1986 minus weight at age 21) was not associated with total prostate cancer (RR = 0.89, 95% CI = 0.69-1.16 for a weight gain of 40 pounds or more relative to weight maintenance within 5 pounds, controlling for age and BMI at age 21; \( P_{\text{trend}} = 0.35 \)) nor with advanced prostate cancer (RR = 0.98, 95% CI = 0.64-1.49; \( P_{\text{trend}} = 0.79 \)). The null relation with adult weight gain did not vary by age.

In contrast to BMI in 1986, a higher BMI at age 21 was strongly related with a decreased risk of advanced and metastatic prostate cancer, adjusting for height and BMI in 1986 (Table 2). Further adjustment for dietary variables, vasectomy, smoking, alcohol, and race did not alter the RRs. Total prostate cancer was not appreciably related to BMI at age 21.

We next examined height in 1986 in relation to risk of prostate cancer (Table 3). For total prostate cancer, we found a slight direct association between height and risk of prostate cancer, although the association was not statistically significant (\( P = 0.12 \)) after adjusting for BMI in 1986 and at age 21. For the advanced or metastatic lesions, a stronger positive association was noted: men who were ≥74 inches tall were at 60-70% greater risk of being diagnosed with the more advanced forms of the disease than were men who were ≤68 inches tall.

We examined waist and hip circumference measures assessed in 1987 in relation to prostate cancer risk. Among men who met inclusion criteria, 30,966 provided data on this in 1987. No appreciable association was noted for waist circumference, but an inverse association was noted between hip circumference and total, advanced, and metastatic prostate cancer (Table 4). The inverse association between hip circumference and risk of metastatic prostate cancers persisted when we added BMI in 1986 to the model (RR = 0.47 with 95% CI = 0.22-1.01, between high and low quintiles; \( P_{\text{trend}} = 0.05 \)), but it became attenuated and nonsignificant when we controlled BMI at age 21 years (RR = 0.70 with 95% CI = 0.39-1.25; \( P_{\text{trend}} = 0.23 \)).

We explored further the inverse association between obe-
sity at a younger age and risk of prostate cancer by using the self-assessment of body adiposity. In 1988, the participants reported their body build at age 5, 10, 20, 30, 40, and age in 1988 using a series of nine pictograms, which ranged subjectively from very lean to very obese. These self-reported assessments were used to form approximate quintiles or quartiles (when the distribution was narrow) for the various ages. Higher reported level of adiposity at ages 5, 10, and 20 years was associated with a lower risk of prostate cancer, particularly for metastatic lesions (Table 5). Specifically, men who in 1988 reported greater adiposity at ages 10 and 20 had approximately one-third of the risk of advanced prostate cancer as the leanest men. Because of high correlations among the body build assessments at ages 5, 10, and 20, it is difficult to separate the independent effect of obesity for each age (Spearman correlation = 0.92 between adiposity at ages 5 and 10, 0.80 between 5 and 20, and 0.87 between 10 and 20). Nonetheless, when we modeled various combinations of adiposity at the different ages, obesity at age 10 was the strongest predictor of reduced risk (RR = 0.41, with 95% CI = 0.14–1.25, when adjusted for adiposity at age 5, and RR = 0.18, with 95% CI = 0.18–0.96, when adjusted for adiposity at age 20). There were suggestive inverse associations also with measures of adiposity at ages 30 and 40. However, when controlled for adiposity at age 10, the relationships with adiposity at ages 30 and 40 did not persist, whereas the inverse association at age 10 remained significant.

We conducted an analysis using the 1988–1994 follow-up among men who had no prostate cancer at baseline in 1988 but reported having had a recent digital rectal examination on the 1988 questionnaire, the only common screening test for prostate cancer at the time. We would expect that newly diagnosed cases of metastatic prostate cancer would represent particularly aggressive forms of the disease because they did not have clinically detectable disease in 1988. In this analysis, we found that obesity at age 10 had a strong inverse association (RR = 0.16 with 95% CI = 0.05–0.54, between high and low quintiles), and tallness had a strong direct association with risk of metastatic disease (RR = 2.29 with 95% CI = 1.04–5.05, for height of ≥74 inches versus ≤68 inches). Neither obesity nor height predicted organ-confined (stage A or B) disease (RR = 0.89 with 95% CI = 0.63–1.26, and RR = 1.16 with 95% CI = 0.77–1.76, for obesity at age 10 and height, respectively).

**Discussion**

Tallness was a marker of increased risk, whereas greater adiposity between the ages of 5 to 20 years was associated with a lower risk of prostate cancer, particularly for advanced disease.
In contrast, anthropometric measures of adult obesity were not independently related to risk of this malignancy. The reported measures of adult BMI, height, and waist and hip circumference were quite precise (30). The self-reported anthropometric measures of earlier periods in life using the body build illustrations have been found to provide useful information, but they have some degree of measurement error, with correlations with direct measures ranging mostly between 0.5 and 0.7 (36). Because of the prospective design, measurement error is likely to be nondifferential with regard to outcome, and thus, the relationships we observed with preadult obesity probably were attenuated by measurement error.

BMI, which is correlated with lean body mass as well as fat mass (39), is a less than ideal measure of adiposity to study the androgen-sensitive prostate because muscle mass is related to androgens (21). However, in our study, adult circumference measures, which may be more strongly related to endocrine abnormalities typically associated with obesity (1), were not appreciably related to prostate cancer risk. A lower risk of prostate cancer was suggested only with greater hip circumference, although this relationship became attenuated and was not statistically significant when adjusted for BMI at age 21. Of note, in one small study, an inverse correlation with free testosterone was stronger for hip circumference \((r = -0.78)\) than for waist circumference \((r = -0.64)\), waist:hip ratio \((r = -0.05)\), or BMI \((r = -0.47); \text{Ref. } 1\). Previous studies have inconsistently found BMI to be associated with a higher risk of prostate cancer, but in at least one study, this was due to the lean mass component of BMI. The overall data, including our results, do not suggest adult adiposity correlates with higher risk of prostate cancer. Possibly, the variation in results could result in part to population differences (e.g., due to age range of the specific population) that determine whether BMI correlates more strongly with lean body mass or with adiposity.

The relationship between height and prostate cancer risk is supported by most, but not all, studies. Four recent studies, including ours (26–28), have found a moderately higher risk of prostate cancer among taller men. Two case-control studies conducted in the early 1970s reported no association between height and risk of this cancer (14, 19). However, inspection of one of these studies (from Fig. 8 in Ref. 14), which did not present odds ratios, showed an excess of cases relative to controls among men 5 feet, 8 inches tall (the median) or taller. Data examining other preadult exposures and risk of prostate cancer are sparse. Two case-control studies in Sweden (27) found that men who were less than 14 years of age at onset of beard growth were at higher risk of prostate cancer, and the authors also found a direct association between height and prostate cancer risk. These findings on early pubertal development and height are in general concordance.
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with our results. The Swedish study found only a weak inverse association between BMI at age 20 and prostate cancer risk, an association that did not persist in multivariate analysis. However, that study had limited range in BMI because only 3 kg/m² separated upper and lower categories, in comparison to 6 kg/m² in our study, and it did not report on the risk for more advanced lesions. This limited range in BMI may have reflected less overall obesity, which would render BMI more a measure of lean body mass than of adiposity. One case-control that assessed various physical characteristics believed to be related to sex hormones during physical examinations in college men did not find any obvious relation with prostate cancer risk (19). However, because these men were of college age, events around the time of puberty may not have been adequately assessed.

Our findings regarding anthropometric measures may be related to the profound hormonal changes that begin at puberty. Height is determined by genetic and nutritional factors, mediated largely through the endocrine system. At puberty, levels of both testosterone and IGF-I rise dramatically. Although the determinants of height are complex, men who attain a greater height may have been exposed to higher levels of IGF-I and testosterone during a critical growth period in general and for the prostate gland specifically. Obesity in males is associated with endocrine aberrations, including higher estrogen and lower testosterone levels (1–6). Lower level of growth hormone, a major determinant of IGF-I levels, has also been associated with both preadult and adult obesity (40–42). These hormonal changes may reflect either a cause or a consequence of obesity, but some of these changes are at least partially reversible through weight loss (42).

The prostate gland is essentially dormant until puberty, when a complex interaction between sex and other growth hormones, as well as their binding proteins, induces its development. Prostatic growth is controlled by serum testosterone, which is converted intracellularly by 5-α-reductase to dihydrotestosterone (43). Androgens may sensitize hormone-dependent tissue to the effects of IGF-I and may increase IGF-I production at the time of puberty (44). Prostate epithelial cells have IGF-I receptors, and IGF-I stimulates mitogenicity in prostate cell lines (45–48) and increases activity of 5-α-reductase (49). By stimulating prostatic epithelial cell division, these same hormonal factors may be critical in carcinogenesis. Thus, prostate cancer occurs rarely in castrated men (50), and the prolonged administration of high levels of testosterone induces prostate cancer in rats (51, 52). Moreover, higher testosterone levels increase risk of prostate cancer, whereas higher levels of sex hormone binding globulin, which renders testosterone inaccessible, may be protective (7).

Relationships among preadult obesity, testosterone levels, and development of gonads and secondary sex organs are supported in animal studies. Rats that are homozygous for the corpulent gene (cp/cp), characterized by marked hyperphagia, obesity, and hyperinsulinemia (53), may be a relevant model. Male cp/cp rats demonstrate delayed puberty, marked reduction in the characteristic rise of testosterone levels at puberty, and decreased organ weights for testes and seminal vesicles. By sexual maturity, the weight of the testes catches up to normal, but the levels of testosterone remain about only one-third that of normal levels. Moreover, seminal vesicle size also remains abnormally small.

Inadequate nutritional intake before adulthood will stunt overall growth and organ cellularity (54). The members of populations that experience some degree of energy restriction during the prepuberty period would tend to be shorter on average and to experience lower stimulation from growth-enhancing hormones, such as IGF-I (55). On the basis of international correlational data, these populations are at lower risk of prostate cancer mortality (56). Because our population of health professionals is unlikely to have experienced substantial undernourishment, the lower rate of advanced prostate cancer among shorter men may reflect lower levels of growth-related hormones more closely related to genetic factors than to severe energy restriction. Because obesity is more prevalent in developed countries, it may appear paradoxical that preadult obesity protects against the occurrence of prostate cancer. However, within a uniformly adequately nourished population, obesity in individuals may be related to a hormonal milieu, including low testosterone and IGF-I and high estrogen, which may lower risk of this malignancy.

The hormonal milieu associated with linear growth and preadult obesity may influence risk of advanced prostate cancer, but the mechanism at the cellular or genetic level is unknown. Perhaps a higher level of androgens and other growth factors present during the development of the prostate gland increases the pool of stem cells at risk, or increases the mitotic rate, which may enhance the likelihood of the occurrence and propagation of a genetic mistake. Our findings were limited to aggressive forms of prostate cancer, suggesting that some preadult hormonal factors influence only a subset of prostatic cancers, which have the potential for rapid progression, or that some of the factors which determine aggressive behavior are "programmed" early during carcinogenesis. At this point, these possibilities are only theoretical, with little supporting evidence.

Our findings suggest that the prepupal hormonal milieu, as reflected in attained height and obesity, may have a profound influence on prostate carcinogenesis. Although these results are of interest in understanding prostate carcinogenesis, the impact of adolescent obesity on overall health status is adverse (57). The concept that aggressive behavior of a tumor is strongly determined by hormonal stimulation during organ development deserves further study.

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References


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