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Notes

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Body Size and Prostate Cancer: a 20-Year Follow-up Study Among 135 006 Swedish Construction Workers

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Background: **Obesity is associated with endocrine changes (e.g., increased estrogen and decreased testosterone in the blood) that have been implicated in the cause of prostate cancer and, therefore, an association between body weight and the risk of developing prostate cancer would be expected. However, because of bias or low statistical power in previous epidemiologic studies, associations between anthropometric measurements (height and weight), body mass index (BMI), and the risk of prostate cancer may have been inadvertently overlooked.** ***Purpose:*** **We performed a large, retrospective cohort study among Swedish construction workers to evaluate possible associations of adult weight, height, BMI, and lean body mass (LBM) by age at entry in the study with the incidence and mortality rate of prostate cancer.** ***Methods:*** **We analyzed data that had been compiled in a computerized central register on a cohort of approximately 135 000 male construction workers. Information on height and weight had been collected with the use of a comprehensive questionnaire filled out by nurses at the time of enrollment in the cohort, from 1971 through 1975. Complete follow-up was achieved through 1991 by means of record linkage to the Swedish National Cancer Register, the Death Register, and the Migration Register. A total of 2368 incident cases and 708 deaths from prostate cancer occurred in the cohort during a follow-up period averaging 18 years. We used only information obtained at the index visit from 1971 through 1975 to determine age-adjusted rate ratios (RRs) in a Poisson-based multiplicative multivariate model with age and the relevant exposure variable (e.g., weight, height, BMI, and LBM) as independent variables.** ***Results:*** **All anthropometric measurements were positively associated with the risk of prostate cancer and were more strongly related to mortality than to incidence. The excess risk of death from prostate cancer was statistically significant in all BMI categories above the reference category: RR = 1.40 (95% confidence interval [CI] = 1.09-1.81) in the highest category compared with the lowest (*P* for trend = .04). For height and LBM, the excess risk in the highest compared with the lowest categories was somewhat less pronounced: RR = 1.28 (95% CI = 1.02-1.60) and RR = 1.26 (95% CI = 1.02-1.57), respectively. Statistically significant linear dose–response relationships were also found with the incidence of prostate cancer, with the exception of BMI (*P* for trend = .10).** ***Conclusion:*** **Our large cohort study indicates that various aspects of body size are related to the risk of prostate cancer and that future studies are needed to study the role of body size and prostate cancer. [J Natl Cancer Inst 1997; 89:385-9]**

The cause of prostate cancer remains unclear (*1*); age, race, and family history are the only established risk factors. The marked variation in the incidence of clinical prostate cancer between different ethnic groups (*2*) and the findings in migrant studies indicate an environmental cause

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See ''Notes'' following ''References.''

for this disease and the importance of exposures in early life (*3*). Although several analytic epidemiologic studies have suggested a role for dietary fat—and animal fat in particular—in the cause of prostate cancer (*4*), several case–control (*5-7*) and cohort (*8-10*) studies provide no support for this theory.

Obesity is associated with endocrine changes, including increased estrogen and decreased testosterone levels, as well as lowered sex hormone-binding globulin in the blood (*11*). Hence, since hormonal factors—notably levels of biologically available androgens—have been implicated in the cause of prostate cancer (*12*), an association between body weight and the risk of developing prostate cancer would be expected. However, body mass index (BMI), which reflects both fat and lean tissues as well as other anthropometric measurements (height and weight), has not been consistently associated with the risk of prostate cancer in previous epidemiologic studies (*1*), but weak associations may have been overlooked because of bias or low statistical power.

We performed a large, retrospective cohort study among Swedish construction workers to evaluate possible associations of adult weight, height, BMI, and lean body mass (LBM) by age at entry in the study with the incidence and mortality rate of prostate cancer.

Subjects and Methods

Cohort

The Construction Industry's Organization for Working Environment, Safety and Health (''Bygghälsan''), a joint venture between trade unions and the Swedish Construction Employer's Association, provided outpatient medical services for construction workers throughout Sweden from 1969 through 1992. The basic units included stationary and mobile clinics, usually staffed by a few nurses and a physician. The main activity was a preventive health checkup, offered to all blue- and white-collar workers in the building industry through regular personal invitations (every second year during the first years, every third year thereafter) and through visits to—or advertisements at—virtually all major building sites. Beginning with visits from 1971, data from these repeated health checkups were compiled in a computerized central register.

We evaluated 135 049 men registered in 1971 through 1975. Forty-three subjects were excluded because of prostate cancer before entry in the cohort or inconsistencies revealed in the analyses (date of death or date of emigration before entry in the cohort), leaving 135 006 subjects for the final analyses. Cohort characteristics are shown in Table 1.

Table 1. Follow-up study of Swedish construction workers*

Age at entry, y	No. of subjects (%)	Person-years of follow-up	Mean (SD)			
			Weight, kg	Height, cm	BMI, kg/m^2	LBM, kg
<30	40 559 (30.0)	746 692	73.0 (9.8)	178.4 (6.2)	22.9 (2.7)	59.9 (4.9)
30-39	30 911 (22.9)	563 660	76.3 (10.1)	176.8 (6.1)	24.3 (2.8)	59.9 (5.1)
40-49	25 364 (18.8)	450 906	77.7 (10.5)	175.4 (6.1)	25.2 (3.0)	59.0 (5.3)
50-59	26 720 (19.8)	440 436	77.9 (10.8)	174.2 (6.0)	25.6 (3.1)	57.6 (5.4)
⩾60	11 452 (8.5)	167 312	76.6 (10.6)	173.0 (5.9)	25.5 (3.1)	55.8 (5.3)

*Number of subjects recruited from 1971 through 1975, accumulated person-years during follow-up with regard to incidence of prostate cancer through 1991, and mean values with standard deviation (SD) for weight, height, body mass index (BMI), and lean body mass (LBM) by age at entry.

On average, each cohort member had three health checkups. In the present analysis, however, we used only information obtained at the index visit during 1971 through 1975, which defined entry in the cohort. Before each visit, the workers answered a comprehensive questionnaire with approximately 200 items pertaining to, e.g., marital status and a detailed smoking history. Four categories were used to classify marital status: married, unmarried, widower, or divorced. Smoking status was classified as current, previous, or never smoked. During the visit to the clinic, the questionnaires were checked by a nurse to avoid misunderstandings and missing or inconsistent answers. Height and weight, measured in a standardized way, were included in each medical record. The quality of the data has been reviewed previously (*13*). Briefly, fewer than 200 persons lacked data on the anthropometric measurements used. On average, each person had three measurements of height. For 79% of the cohort members with more than one measurement, the difference between the highest and the lowest value of height was 1 cm or less, and in 98.5% the difference was 4 cm or less.

Follow-up

Major efforts were made to ensure that the national registration numbers, unique personal identifiers assigned to all residents in Sweden, were complete and valid. The proportion having incorrect national registration numbers was less than 1 in 1000. The national registration number was used for follow-up through linkage to the Cancer Register, which is more than 98% complete (*14*), the Death Register, and the Migration Register. The Cancer Register, founded in 1958, has coded malignant neoplasms according to the International Classification of Diseases, 7th Revision (ICD-7) during the entire period of study. This study reports the incidence of prostate cancer (ICD-7:177) and the mortality with this cancer coded in the Death Register as the underlying cause of death. Each cohort member contributed person-years from the date of the first registered visit, according to the Construction Industry's Organization for Working Environment, Safety and Health database, until the date of diagnosis of prostate cancer (in the incidence analyses), death, migration, or the cutoff date of December 31, 1991, whichever came first. A total of 2368 men in the cohort developed prostate cancer during follow-up through 1991. Altogether, 2 369 006 person-years were observed in the analyses of the incidence of prostate cancer and 2 377 960 in the corresponding analyses of the mortality rate.

Statistical Analyses

Since the risk of prostate cancer is highly age dependent, we first analyzed the age distribution in various exposure categories. Then the number of cases and person-years experienced was computed within 12 age intervals (<30, 30-34, . . . , 75-79, and ⩾80 years) for each category of exposure variable studied. These data were used to obtain the age-adjusted rate ratios (RRs) in a first simple multiplicative multivariate model, with age and the relevant exposure variable as independent variables. Because of small risk of prostate cancer at younger ages, age was included with nine categories (<45, 45-49, . . . , 75-79, ⩾80) in the modeling. The modeling was based on the assumption that the number of cases followed a Poisson distribution. The models were fitted using the maximum likelihood method (*15*). On the basis of the results thus obtained, further multivariate modeling was then performed. In addition to each of the main variables (height, weight, etc.), these models included age, smoking status, and marital status. These variables were considered to be the most important possible confounding variables among those variables for which we had data. Multivariate models with several of the main variables (height, weight, BMI, and LBM) were not considered, since the high correlation between these variables makes it impossible to obtain results with sufficient precision. Results for the explanatory variables are reported with the variables in categorized form. For the body size measurements, categories based on approximate quartiles were used. Since the data for the basic variables of height and weight were available in whole centimeters and kilograms, the limited number of scale steps means that exact quartiles cannot be obtained. The trend tests are based on categorized variables with the categories coded as 1, 2, 3, and 4. BMI was calculated as weight/height^2 (kg/m^2). LBM, an estimate of body components that are not adipose, was calculated as [2.447 − 0.09516 age (years) + 0.1074 height (cm) + 0.3362 weight (kg)] divided by 0.732 (*16,17*).

Results

The age-adjusted RRs by different anthropometric measurements are shown in Table 2. These were obtained from multivariate Poisson models with age included, in addition to each of the variables shown. The fact that the risk of prostate cancer is strongly age dependent and that several of the explanatory variables were

related to age means that the age-adjusted relative risks shown in many cases deviate substantially from the unadjusted relative risks that can be inferred from the number of cases and person-years shown in Table 2.

Overall, a positive association with a risk of prostate cancer was observed for all of these measurements; the risk was slightly (13%-17%) higher in the highest compared with the lowest category of weight, height, BMI, and LBM. The trend was statistically significant for all measurements, except BMI. Further multivariate analyses of BMI, including smoking and marital status, did not materially affect the estimates shown in Table 2 (e.g., RR = 1.15; 95% confidence interval [CI] = 1.01-1.32 for the highest quartile of BMI).

Table 3 presents age-adjusted relative risks of death from prostate cancer in relation to the different anthropometric measurements. A total of 708 deaths was observed during the follow-up period. All individual measurements were positively associated with death from prostate cancer and, indeed, were consistently more strongly related to death than to the incidence of prostate cancer.

For BMI, the increase in risk was statistically significant at the 5% level in all categories above the reference category (RR = 1.40 for the highest category; 95% CI = 1.09-1.81; *P* for trend = .036). For weight, height, and LBM, the excess risk in the highest categories was somewhat less, although the dose–response trends were statistically significant for all variables.

Table 2. Incidence of prostate cancer among Swedish construction workers in relation to weight, height, body mass index (BMI), and lean body mass (LBM) analyzed as categorized variables*

Variable	No. of subjects	Person-years	No. of cases	RR	95% CI
Weight, kg					
<69	32 798	580 277	448	1.0	Referent
69-75	37 491	662 693	606	1.05	0.93-1.19
76-82	32 348	566 563	588	1.04	0.92-1.17
>82	32 242	557 334	722	1.16	1.03-1.31
			P for trend = .02		
Height, cm					
<172	31 026	528 898	792	1.0	Referent
172-176	39 910	698 122	770	1.05	0.95-1.16
177-180	30 613	542 425	458	1.07	0.96-1.21
>180	33 287	596 622	345	1.14	1.00-1.29
			P for trend = .04		
BMI, kg/m^2					
<22.1	33 132	594 215	290	1.0	Referent
22.1-24.1	34 758	617 332	499	1.09	0.94-1.26
24.2-26.2	33 600	587 500	676	1.10	0.96-1.26
>26.2	33 325	566 678	899	1.13	0.99-1.29
			P for trend = .10		
LBM, kg					
<55.00	30 888	527 165	834	1.0	Referent
55.01-58.5	35 265	620 195	614	1.08	0.97-1.19
58.6-62	33 702	597 972	489	1.16	1.03-1.29
>62	34 960	620 394	427	1.17	1.04-1.32
			P for trend = .002		

*Age-adjusted rate ratios (RRs) are given with the 95% confidence intervals (CIs) obtained from multivariate Poisson models, which include adjustment for age in each case.

Discussion

Our cohort study of about 135 000 male construction workers, followed for an average of 18 years, revealed a positive association of weight, height, BMI, and LBM with the risk of prostate cancer. Analyses confined to fatal—i.e., biologically aggressive—cancers showed that all body-size indicators were more strongly associated with death from—than incidence of—prostate cancer. Since most of the anthropometric variables were highly correlated, one could not discern the effect of each specific variable.

The validity of our data is considered high. Selection or information bias is not likely. Since all measurements were standardized, nondifferential misclassification, which would attenuate the associations, should be minimal. Furthermore, the zealous checks of the national registration numbers among cohort members and the estimated 98% completeness of the Cancer Register (*18*) ensured an almost complete follow-up. Although the

Table 3. Mortality from prostate cancer among Swedish construction workers in relation to weight, height, body mass index (BMI), and lean body mass (LBM) analyzed as categorized variables*

Variable	Person-years	No. of deaths	RR	95% CI
Weight, kg				
<69	581 998	131	1.0	Referent
69-75	664 886	170	1.03	0.82-1.29
76-82	568 722	167	1.03	0.82-1.30
>82	560 196	240	1.34	1.08-1.66
			P for trend = .002	
Height, cm				
<172	532 186	241	1.0	Referent
172-176	700 920	216	0.99	0.82-1.18
177-180	544 077	137	1.08	0.88-1.34
>180	597 823	114	1.28	1.02-1.60
			P for trend = .04	
BMI, kg/m^2				
<22.1	595 307	74	1.0	Referent
22.1-24.1	619 104	155	1.36	1.03-1.79
24.2-26.2	589 958	202	1.33	1.02-1.74
>26.2	570 292	277	1.40	1.09-1.81
			P for trend = .04	
LBM, kg				
<55.00	530 357	247	1.0	Referent
55.01-58.5	622 458	167	1.02	0.84-1.24
58.6-62	599 869	166	1.38	1.14-1.69
>62	621 977	128	1.26	1.02-1.57
			P for trend = .002	

*Age-adjusted rate ratios (RRs) with 95% confidence intervals (CIs) were obtained from multivariate Poisson models, which include adjustment for age in each case.

implications of chance effects can be estimated, the potential effect of confounding is more problematic, especially in studies of prostate cancer, because risk factors are incompletely known. Our analyses were age adjusted, the cohort members were almost all Caucasians, and the relative occupational homogeneity of the construction workers may reduce confounding by unmeasured factors. Confounding by, for example, dietary factors is conceivable, although a recent large case–control study in Sweden (*7*) failed to reveal any important dietary determinants of the risk of prostate cancer in the Swedish population. Dietary fat intake in adult life plays a role in prostate cancer, according to several, but not all, previous epidemiologic studies (*19*). If dietary fat (or some components of it) is causally linked with prostate cancer, then a positive confounding effect on weight and BMI is possible; confounding of the association with height and LBM appears more tenuous, since height is determined during adolescence and LBM is independent of body fat.

The possible relation between anthropometric measurements and risk of prostate cancer has been evaluated in several previous reports with inconsistent findings. No association between BMI, weight, and the risk of developing prostate cancer was found, particularly in studies with a case–control design (*6,20-27*), while support for a positive association is derived mostly from cohort studies (*28-31*) and some case–control studies (*32,33*). In most case–control studies, the analyses were based on self-reported anthropometric measurements at the time of diagnosis. Some patients may have lost weight because of the disease; this could partly explain the lack of an association between BMI and the risk of prostate cancer in some investigations.

The weak positive association between BMI—a measure of obesity—and the risk of prostate cancer found in our study could be plausibly explained by several mechanisms. First, obesity is associated with several hormonal aberrations in men, including higher estrogen and lower testosterone levels (*11*). Obesity also entails lower levels of sex hormone-binding globulin, which should increase mainly the fraction of biologically available testosterone. Since sex hormones, especially androgens, have been implicated in the cause of prostate cancer, the endocrine aberrations associated with obesity may play a role in the cause of this disease (*19*). In addition, the role of other associated endocrine aberrations (e.g., hyperinsulinemia) and the relation between different body fat distribution and hormone metabolism is still not fully understood. Second, high BMI may reflect an imbalance between caloric intake and physical activity. High energy intake and low physical activity have been thought to be positively associated with risk of prostate cancer (*6,7,34,35*).

A third hypothesis relates to the suggested positive association between obesity and sympathetic activity (*36*). In an animal study (*37*), the balance between local sympathetic and parasympathetic activity influenced growth of the prostate gland. This mechanism may involve the cell-growth stimulating effect of local growth factors, such as epidermal growth factor, nerve growth factor (NGF), or insulin-like growth factor-1 (IGF-1). Adrenergic neurotransmitters have been reported to increase NGF synthesis in nonneuronal tissues (*38*) and circulating levels of IGF-1 were reduced by caloric and protein restriction in humans (*39-41*). Resting heart rate, an indicator of sympathetic activity, was associated with the mortality rate from prostate cancer in one study (*42*). Among patients with schizophrenia, the incidence of prostate cancer was reduced by 44% among those treated with chlorpromazine, a drug with markedly antiadrenergic properties (*43*). Thus, obesity may be involved in prostate carcinogenesis through a relation with sympathetic activity.

BMI reflects both lean tissues and body fat. In a prospective study (*29*), a positive association between BMI and prostate cancer was ascribed to greater muscle mass among case subjects, perhaps because of an excess of androgens, rather than to adiposity. Therefore, LBM may be more relevant than BMI in studies of androgen-dependent disorders, such as prostate cancer, in an elderly population. However, the calculated LBM index may not be correct because the formula assumes that the proportion of water in the LBM is constant. In reality, this proportion varies, depending on the state of hydration and the relative subcomponents of this mass. Moreover, the validity of the equation predicting total body water for men is not perfect ($r = .84$), since it can vary between populations (*16,17*). These limitations of the index would most likely entail nondifferential misclassification and therefore underestimation of the time association between LBM and prostate cancer.

Only one previous epidemiologic investigation—a cohort study (*44*)—found a positive association between height and risk of prostate cancer, with an 80% higher risk among men in the third and fourth quartiles of height compared with the lowest quartile (P for trend = .01). Adult height is determined by nutritional status during childhood and adolescence and by genetic influences. IGFs are vital for normal growth and development during fetal, neonatal, and pubertal stages (*45*). The production of IGF-1 may be stimulated by sex steroids at the time of puberty, and in prepubertal boys, testosterone dramatically increases the level of plasma IGF-1 (*46*), which correlates with growth in childhood and adolescence (*47*). Moreover, IGF-1 levels are reduced by lowering the energy and protein intake in humans (*39-41*). Thus, one candidate mediator of the positive association between height and prostate cancer is definitely IGF-1, the actions of which deserve further evaluation.

In summary, our large cohort study shows that various aspects of body size are related to the risk of prostate cancer. Since anthropometric measurements reflect nutritional, hormonal, neuroendocrine, and other factors during various periods of life, much more research is needed to clarify precisely the mechanisms by which these factors may influence carcinogenic processes in the prostate. Anthropometric measures were consistently more strongly associated with mortality than with incidence RRs of prostate cancer. If these quantitatively small differences hold up in future studies, one might speculate that measures of body size—or their determinants—play a role in the progression from latent to aggressive prostate cancer.

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Notes

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