Body Size and Prostate Cancer

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ANTHROPOMETRY AND BODY FAT DISTRIBUTION

Anthropometry is the branch of anthropology that deals with the comparative measurements of the human body and its associated parts. It is the most widely utilized and least expensive method of assessing human body composition. In epidemiologic and clinical studies, it is mainly used to calculate body fatness and fat-free mass in groups and individuals (1). Anthropometric measurements to estimate obesity include weight, weight in relation to height, skinfold thicknesses, and circumference measurements of the trunk and limbs (2).

Body fatness reflects the interaction of human growth and development with the environment under the influence of a person's genotype. Studies in twins, other biologic relatives, and relatives by adoption show that about 25 percent of the variance in percent body fat is attributed to genetic factors after adjustment for age and gender differences (3). Inheritability is estimated to be as high as 30-40 percent for factors such as adipose tissue distribution, resting metabolic rate, lipoprotein lipase activity, and basal rates of lipolysis (4). At the same time, the rising prevalence of obesity in the United States and the secular trend toward increasing obesity present clear evidence of the environmental influences on adiposity (5-7).

Investigations of the relation between body size and prostate cancer have focused mainly on weight and measurements of obesity, such as the body mass index (BMI). The BMI, which is defined as body weight in kilograms (kg) divided by the square of the height in meters (m²), is a surrogate for body fat content (8). It is highly correlated with percent body fat determined hydrostatically by total body submersion (9). This index has been commonly used since it has frequently been shown that persons with a high body mass relative to stature have high mortality rates (10-12).

In spite of its popularity, there are limitations of BMI as an objective measure of obesity, as pointed out by Garn et al. (13). Firstly, the assumption that the BMI is independent of stature is not entirely true for adults and especially not true for children. Secondly, persons with short legs for their height have higher BMI values, which indicates the extent to which BMI is also a measure of body build or body proportion. Lastly, BMI reflects both body fatness and lean body mass.

Another point to consider in epidemiologic studies is the source of the data regarding weight and height. Although self-reported weight and height are generally highly correlated with measured weight and height, the magnitude of the correlations can vary across studies (2). Furthermore, high correlations do not necessarily reflect accuracy, because systematic differences between self-reported and measured values may exist in spite of the strength of the correlations. Biases in self-reported weight and height have been documented (14, 15). Men tend to under-report their weight when they are obese and over-report it when they are underweight.

In recent years, the distribution of body fat has received more attention as an important dimension in studying the relation between obesity and health. Persons with excess fat stored mainly on the upper body (male or android obesity) have been shown to have an increased risk for total mortality, cancer, and cardiovascular disease (16-18). Waist circumference or the ratio of waist to hip circumferences have been used to estimate upper body fat (8). However, there are problems in using circumferences as indices of adipose tissue distribution because standard definitions of the circumferences are not always followed. The "waist" circumference has been variously defined as the umbilicus, the lower margin of the ribs, the iliac crests, and at the level of the smallest circumference on the torso below the sternum. Similarly, the "hip" circumference has been set at the iliac crests, the anterior iliac spines, the greater trochanter of the femur bone, or the maximum posterior protrusion of the buttocks (2). There may be appreciable differences among circumferences measured at these locations, and these bony landmarks may be difficult to identify in obese persons.

In addition to BMI and body fat distribution, another measure of human obesity that is of interest is abdominal visceral fat. Its amount is important in determining whether obesity has major or minor health implications in an individual (19). As with estimating upper body fat, a waist circumference measurement can provide reasonable mean values of abdominal visceral fat for a group, but it is not accurate for a given individual (8). A computed tomography scan or magnetic resonance imaging is needed to measure abdominal visceral fat accurately.

Besides obesity, height or stature is another measurement used to evaluate body size in relation to health. Adult height or stature is determined primarily by two components, heredity (parental stature) and nutritional intake during the
developmental period (20). As such, height is a potentially important marker of the effects that early nutrition may have on human carcinogenesis.

**BODY SIZE AND PROSTATE CANCER**

A number of studies have been done to assess the relation of body size to prostate cancer. These investigations have usually used anthropometric measurements in describing their findings. Table 1 summarizes the results from 12 case-control studies which were conducted from 1986 to 1999 (21–32). The investigations were done in Greece, the United States, Sweden, Canada, South Africa, and Italy; 10 of them reported no significant association between prostate cancer and various measurements, including weight, height, BMI, waist/hip ratio, waist circumference, and triceps skinfold thickness. The number of cases in these studies ranged from 120 to 1,655. The sources of controls was variable as there were seven studies with population controls, two with hospital or clinic controls, and one with neighborhood controls. Six of the 10 studies collected interview data, three examined the study participants, and one obtained questionnaire data.

In the two studies that reported a positive association (23, 32), the odds ratios were 1.9 and 3.9, respectively, based on the BMI in the highest quantile group. Gronberg et al. (23) identified 406 prostate cancer cases from the Swedish Twin Registry, and used the same registry to select 1,218 unrelated controls who completed the same questionnaire. Talamini et al. (32) interviewed 166 cases and 202 hospital controls in northern Italy and found that 68 cases, compared with 44 controls, had a BMI of 28 or greater.

In many case-control studies the analysis depended upon self-reported anthropometric measurements, which may have limitations as pointed out earlier. Some patients may have lost weight because of their disease, which could limit the validity of measuring weight at time of examination in case-control studies. Cohort studies, in which the participants were examined for their anthropometric measurements before they were subsequently diagnosed with prostate cancer, have an obvious advantage over case-control studies in this regard.

**TABLE 1. Summary of results from case-control studies of anthropometry and prostate cancer**

<table>
<thead>
<tr>
<th>Study (reference no.), year, location</th>
<th>No. of subjects</th>
<th>Measurement</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hsieh et al. (21), 1999, Athens, Greece</td>
<td>320 cases; 246 hospital controls</td>
<td>BMI*, height</td>
<td>No significant differences</td>
<td>Interview data</td>
</tr>
<tr>
<td>Demark-Wahnefried et al. (22), 1997, North Carolina</td>
<td>159 cases; 156 urology clinic controls</td>
<td>BMI</td>
<td>OR* = 0.9 (NS*)</td>
<td>Examination data</td>
</tr>
<tr>
<td>Gronberg et al. (23), 1996, Sweden</td>
<td>406 cases; 1,218 controls</td>
<td>BMI</td>
<td>OR = 1.9 (p = 0.002)</td>
<td>Questionnaire data; cases and unrelated controls are in twin registry</td>
</tr>
<tr>
<td>Ghadirian et al. (24), 1996, Montreal, Canada</td>
<td>232 cases; 231 population controls</td>
<td>BMI</td>
<td>OR = 1.0 (NS)</td>
<td>Interview data</td>
</tr>
<tr>
<td>Rohan et al. (25), 1995, Ontario, Canada</td>
<td>207 cases; 207 population controls</td>
<td>BMI</td>
<td>OR = 1.1 (NS)</td>
<td>Interview data</td>
</tr>
<tr>
<td>Whittemore et al. (26), 1995, United States; Canada</td>
<td>1,655 multiethnic cases; 1,645 population controls</td>
<td>BMI, waist circumference, weight, height</td>
<td>No significant differences</td>
<td>Interview data; mean values for cases and controls were reported</td>
</tr>
<tr>
<td>Andersson et al. (27), 1995, Sweden</td>
<td>256 cases; 252 population controls</td>
<td>BMI</td>
<td>OR = 0.6 (NS)</td>
<td>Examination data</td>
</tr>
<tr>
<td>Gann et al. (28), 1994, United States</td>
<td>120 physician cases; 120 physician controls</td>
<td>BMI</td>
<td>No significant difference</td>
<td>Questionnaire data; mean values for cases and controls were reported</td>
</tr>
<tr>
<td>Walker et al. (29), 1992, South Africa</td>
<td>166 cases; 166 neighborhood controls</td>
<td>BMI, height</td>
<td>No significant differences</td>
<td>Examination data; mean values were reported</td>
</tr>
<tr>
<td>West et al. (30), 1991, Utah</td>
<td>358 cases; 679 population controls</td>
<td>BMI</td>
<td>Calculated OR = 1.0 (NS)</td>
<td>Interview data</td>
</tr>
<tr>
<td>Kolonel et al. (31), 1988, Hawaii</td>
<td>452 cases; 899 population controls</td>
<td>BMI, weight, height</td>
<td>No significant differences</td>
<td>Interview data; mean values were reported</td>
</tr>
<tr>
<td>Talamini et al. (32), 1986, northern Italy</td>
<td>166 cases; 202 hospital controls</td>
<td>BMI</td>
<td>OR = 3.9 (p = 0.006)</td>
<td>Interview data; no differences in height between cases and controls</td>
</tr>
</tbody>
</table>

* BMI = body mass index; OR = odds ratio for the highest quantile; NS = not significant.

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Table 2 presents a review of the data from 11 cohort studies published from 1984 to 2000 (33-43). The results are mixed. Five of the reports suggested that there was a positive association of prostate cancer with either body mass index, lean body mass, weight, or percent desirable weight (36, 37, 40, 41, 43). The findings with regard to height will be discussed below. The six studies that showed no association reported on either BMI, lean body mass, weight, waist-to-hip ratio, or triceps skinfold thickness (33-35, 38, 39, 42). Five (34-37, 41) of the 11 investigations examined the subjects for their anthropometric measurements. Three of these studies (36, 37, 41) found a positive association with either body weight or BMI (relative risk = 1.3-2.2). Two of these studies (36, 37, 41) found a positive association with prostate cancer cases, as the outcome. They both found positive risks ranging from 1.3 to 1.8 in these investigations. Of the five studies that examined their subjects, just one (36) showed a positive relation. Two (36, 38) of the three positive studies had death or advanced disease as the outcome. However, these findings are tempered by the fact that six of the other cohort studies reported no association. Furthermore, none of the six case-control studies in table 1 that reported on height found any association.

Because lean body mass has also been correlated with BMI, researchers examined the association of the former with prostate cancer in three of the studies listed in table 2. Andersson et al. (36) found a positive association (relative risk = 1.3), while the other two groups of researchers (33, 35) reported that there was no relation between lean body mass and prostate cancer risk. Earlier, it was observed that severity of disease may be an important factor, since the majority of cases with prostate cancer do not die from their disease.

The findings for height are even more uncertain than the findings of the other anthropometric measurements in the cohort studies. Three (36, 38, 40) of the nine studies in table 2 that included height reported a positive association. The relative risks ranged from 1.3 to 1.8 in these investigations. Of the five studies that examined their subjects, just one (36) showed a positive relation. Two (36, 38) of the three positive studies had death or advanced disease as the outcome.

TABLE 2. Summary of results from cohort studies of anthropometry and prostate cancer

<table>
<thead>
<tr>
<th>Study (reference no.), year, location</th>
<th>No. of subjects</th>
<th>Measurement</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Shuman et al. (33), 2000, The Netherland</td>
<td>58,279 men; 681 cases</td>
<td>BMI*</td>
<td>RR* = 0.9 (NS)*</td>
<td>Questionnaire data; no association for advanced cases; BMI at age 20 years had positive association (RR = 1.3)</td>
</tr>
<tr>
<td>Habel et al. (34), 2000, California</td>
<td>70,712 men; 2,079 cases</td>
<td>BMI</td>
<td>RR = 0.9 (NS)</td>
<td>Examination data</td>
</tr>
<tr>
<td>Lund Nilsen and Vatten (35), 1999, Norway</td>
<td>22,248 men; 642 cases</td>
<td>BMI</td>
<td>RR = 1.0 (NS)</td>
<td>Examination data; suggestion of weak positive association with height</td>
</tr>
<tr>
<td>Andersson et al. (36), 1997, Sweden</td>
<td>135,006 men; 708 deaths</td>
<td>BMI</td>
<td>RR = 1.4 (p = 0.04)</td>
<td>Examination data; 2,369 incident cases also show positive, but weak associations</td>
</tr>
<tr>
<td>Veerod et al. (37), 1997, Norway</td>
<td>25,708 men; 72 cases</td>
<td>BMI</td>
<td>RR = 2.2 (p = 0.02)</td>
<td>Examination data</td>
</tr>
<tr>
<td>Giovannucci et al. (38), 1997, United States</td>
<td>47,781 professional men; 1,369 cases</td>
<td>BMI</td>
<td>RR = 0.8 (NS)</td>
<td>Questionnaire data; positive association with height (RR = 1.7) in advanced cases</td>
</tr>
<tr>
<td>Cerhan et al. (39), 1997, Iowa</td>
<td>1,050 men, 71 cases</td>
<td>BMI</td>
<td>RR = 1.5 (p = 0.10)</td>
<td>Interview data</td>
</tr>
<tr>
<td>Le Marchand et al. (40), 1994, Hawaii</td>
<td>20,316 multiethnic men, 198 cases</td>
<td>BMI</td>
<td>RR = 0.7 (NS)</td>
<td>Interview data</td>
</tr>
<tr>
<td>Chyou et al. (41), 1994, Hawaii</td>
<td>7,840 Japanese men; 306 cases</td>
<td>BMI</td>
<td>RR = 1.5 (p = 0.008)</td>
<td>Examination data</td>
</tr>
<tr>
<td>Mills et al. (42), 1989, California</td>
<td>14,000 Seventh Day Adventists; 180 cases</td>
<td>BMI</td>
<td>RR = 1.2 (NS)</td>
<td>Mailed questionnaire data</td>
</tr>
<tr>
<td>Snowden et al. (43), 1984, California</td>
<td>6,763 Seventh Day Adventists; 84 deaths</td>
<td>TSR</td>
<td>RR = 2.4 (p &lt; 0.01)</td>
<td>Questionnaire data</td>
</tr>
</tbody>
</table>

* BMI = body mass index; LBM = lean body mass; RR = relative risk for the highest quantile; NS = not significant.
the area of muscle in the arm, but not the area of fat in the arm, was positively related to prostate cancer risk (44). However, this finding has yet to be replicated by other researchers.

Overall, the results on BMI are inconsistent. In addition, this index is related to both lean body mass and body fat, which leads to limitations in the interpretation of results associated with this index. Although the distribution of body fat is also an important consideration, only three studies (22, 26, 38) in tables 1 and 2 combined have included measurements in waist circumference or waist-to-hip ratios. They have reported no association of these measurements with prostate cancer. Data are also sparse in assessing whether childhood or infant obesity is more important than adult obesity in relation to prostate cancer. One preliminary study of birth weight followed 366 men and found that high birth weight was associated with prostate cancer in 21 cases (45). However, in another report, obesity at age 10 years, assessed in 33,326 men, was found to be inversely related to the risk of advanced and metastatic prostate cancer (38).

BIOLOGIC MECHANISMS

If obesity is related to prostate cancer, then the biologic pathways are likely to be complex. Obesity has effects on the hypothalamic-pituitary-adrenocortical/thyroid/gonadal axis, as well as on growth hormones, gut hormones, the pancreas, and the sympathetic nervous system in humans (46). It is associated with numerous endocrine changes such as increased estrogen and decreased testosterone levels (47, 48). Obesity leads to lowered sex hormone-binding globulin, which could increase unbound testosterone levels. Researchers have suspected that testosterone is related to prostate cancer risk, but the association has not been established (49).

Obesity is also related to insulin resistance and hyperinsulinemia (50). The syndrome of insulin resistance, or syndrome X, consists of the frequent association of abdominal obesity, hyperinsulinemia, hypertension, dyslipidemia, and accelerated atherosclerosis in the same individual (51). However, no reports have been found on the association between insulin resistance and prostate cancer. Insulin-like growth factors have mitogenic properties and stimulate the growth of normal and tumor cells in the prostate gland (52). Recent studies support the presence of a positive association of insulin-like growth factor-1 with prostate cancer risk (53, 54). Insulin-like growth factor-1 has been positively related to height in children (55), but not in adults (54, 56). Energy intake, BMI, and physical activity affect blood levels of insulin-like growth factors and insulin-like growth factor binding proteins, but their relations are complex and still need to be disentangled (57). The association between insulin-like growth factors and prostate cancer is covered in greater depth in a separate review in this special issue of Epidemiologic Reviews.

The cloning of the Lep gene responsible for obesity in the ob/ob mouse in 1994 led to much interest in the pathophysiology of obesity (58). Leptin, the protein product of the adipocyte-specific ob gene, is believed to have a role in weight regulation and energy expenditure (59). In humans, the place of leptin in the pathogenesis of obesity is unclear. Most obese persons do not have any abnormality in the coding sequence for leptin (60). The production of leptin is increased by insulin and glucocorticoids (61), but the 24-hour profiles of circulating leptin are not correlated with insulin levels (62). It has a circadian rhythm, with serum leptin levels being lowest around noon to mid-afternoon and highest between midnight and early-morning hours. Because of these complexities in the physiology of leptin, it is not surprising that no association was found in a preliminary study of serum leptin in 43 prostate cancer cases and 48 controls (63).

FUTURE RESEARCH

Inexpensive and uninvasive methods to assess adiposity need to be developed to advance our knowledge on the association of obesity with prostate cancer. The BMI has been commonly used, but it has apparent shortcomings in estimating obesity. Bioelectric impedance analysis, as an uninvasive method to estimate percent body fat and lean body mass (64), deserves consideration, although it has limitations in assessing body fat in severe obesity (65). Little attention has been paid to the association of adolescent obesity or body fat distribution with prostate cancer. More information is needed on the possible role of hormones, insulin-like growth factors, and leptin in relation to obesity and prostate cancer risk. Future epidemiologic studies to determine whether body size (obesity) affects prostate cancer risk should include as many of the following features as possible:

1. They should preferably be cohort studies instead of case-control studies, unless the case-control studies have valid data on anthropometric measurements predicting the diagnosis of prostate cancer.
2. The participants should be measured according to established standards, and at least height, weight, waist-to-hip ratio, and skinfold thicknesses should be included in the study. More current anthropometric techniques to measure body fat distribution should be considered.
3. Because of the importance of severity of disease in prostate cancer research, prostate cancer incidence, stage of disease at time of diagnosis, and mortality outcomes should be recorded on participants in cohort studies. However, the problem of competing causes of death and possible information bias in recording the underlying cause of death should be considered in using prostate cancer mortality as the outcome (66).
4. Blood samples should be collected at the time of anthropometric measurements in cohort studies to enable investigators to measure biomarkers that could be helpful in determining whether obesity or related factors are associated with prostate cancer risk.
5. Family history of prostate cancer and relevant gene markers should be included in the study to enable the investigators to assess gene-environment interactions in relation to body size and prostate cancer.
REFERENCES

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