Obesity, metabolic syndrome, and prostate cancer

Ann W Hsing, Lori C Sakoda, and Streamon C Chua Jr

ABSTRACT

Although obesity has been consistently linked to an increased risk of several malignancies, including cancers of the colon, gallbladder, kidney, and pancreas, its role in prostate cancer etiology remains elusive. Data on the association between obesity and prostate cancer incidence are inconsistent, and in some studies obesity is associated with an increase in risk of high-grade prostate cancer but with a decrease in risk of low-grade tumors. In contrast, obesity has been consistently associated with an increased risk of prostate cancer aggressiveness and mortality. The differential effects of obesity on subtypes of prostate cancer suggest etiologic heterogeneity in these tumors and complex interactions between androgen metabolism and several putative risk factors, including insulin resistance, diabetes, inflammation, and genetic susceptibility, on prostate cancer risk. Data on the role of abdominal obesity, insulin resistance, and metabolic syndrome in prostate cancer etiology are limited. Obesity has been shown to be associated with a state of low-grade chronic inflammation, and insulin resistance and the metabolic syndrome are associated with adverse metabolic profiles and with higher circulating concentrations of inflammation-related markers, including leptin, interleukin-6, and tumor necrosis factor-α, many of which have been shown to enhance tumor growth. Thus, whether obesity and metabolic syndrome modulate the risk of prostate cancer through chronic inflammation needs to be investigated further. Given that the prevalence of obesity and metabolic syndrome is increasing worldwide and that the world population is aging, the roles of obesity and metabolic syndrome in prostate carcinogenesis warrant further clarification. Am J Clin Nutr 2007;86(suppl):843S–57S.

KEY WORDS Obesity, abdominal obesity, metabolic syndrome, insulin resistance, prostate cancer

INTRODUCTION

Prostate cancer is the most commonly diagnosed nonskin cancer and the second leading cause of cancer deaths in US men (1–3). Despite the high morbidity associated with prostate cancer, the only established risk factors are age, race, and a family history of prostate cancer (4). However, large geographic variation in prostate cancer risk suggests that lifestyle factors, such as westernization, may also contribute to the etiology of this disease. Men in westernized countries have incidence rates that are 10- to 15-fold those of Asian men (1), although prostate cancer incidence in low-risk Asian countries has risen rapidly in recent years (1, 5, 6). In addition, migrant studies have shown that Asian American men living in the United States have much higher rates (≈50 per 100 000 men-years) than do their counterparts in native lands (10–20 per 100 000 men-years), even though their risk is still much lower than that for white Americans and African Americans (100–150 per 100 000 men-years) (1, 4). The increase in prostate cancer incidence both in Asian countries and in migrants suggests that westernization is an important risk factor for prostate cancer (1, 4).

The biological mechanisms linking westernization to increased prostate cancer risk are unclear. However, it has been hypothesized that the increased prevalence of obesity and metabolic syndrome resulting from lifestyle changes associated with westernization, such as physical inactivity and a higher intake of dietary fat and meat, may explain part of the rising rates in Asian populations. Evidence for the relation between obesity and prostate cancer is inconclusive, and limited data are available on the association between metabolic syndrome and prostate cancer. Because obesity is becoming a pandemic problem and the world population is aging, the impact of obesity on prostate cancer risk needs to be clarified. This review presents current perspectives on the relations of obesity and metabolic syndrome with prostate cancer risk, discusses reasons for the inconsistencies across studies, offers insights into potential biological mechanisms, and suggests directions for future research.

OBESITY AND PROSTATE CANCER

In most epidemiologic investigations, obesity is assessed by body mass index (BMI), which is calculated by weight (kg) divided by height2 (m²) by use of physical measurements or self-reported height and weight. BMI is a marker for overall obesity; it does not differentiate lean from fat body mass, nor does it reflect body fat distribution. Despite the imprecise nature of BMI, it has been consistently linked to several chronic diseases, including cancers of the colon, liver, gallbladder, kidney, and pancreas, but its role in prostate cancer etiology is less clear.

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BMI and prostate cancer incidence

More than 40 studies, including prospective and case-control studies, have examined the role of obesity in prostate cancer etiology (7, 8). In most studies, obesity is defined as a BMI > 30 and overweight is defined as a BMI > 25. In 2001, Nomura (7) reviewed 10 prospective and 12 case-control studies that assessed the role of BMI in prostate cancer and concluded that the evidence is inconclusive. Since then, 14 prospective and 6 case-control studies have tested the hypothesis that obesity is linked to a higher risk of prostate cancer (Figure 1; 9–25). The largest prospective study, which included 950,000 men and 33,314 prostate cancer cases from Norway, reported a 9% excess risk of prostate cancer among obese men (95% CI: 1.04, 1.15), with a more pronounced risk for men who were obese at age 45 y [relative risk (RR) = 1.58; 95% CI: 1.29, 1.94] (10). In a recent meta-analysis that included data from 31 prospective studies and 21 case-control studies, with a pooled estimate of 1.05 (95% CI: 1.01, 1.08) (8). The risk estimates from this meta-analysis were based on both incidence and mortality. When stage of prostate cancer at diagnosis was considered in the analysis, the overall risk for advanced cancer was higher (RR = 1.12; 95% CI: 1.01, 1.23). Collectively, these data suggest that a higher level of usual adult BMI leads to a modest positive effect on total and advanced prostate cancer risk.

Note that certain studies have reported differential effects of BMI on prostate cancer risk. For example, 2 prospective studies showed that obesity is associated with a reduced risk of low-grade prostate tumors, particularly in younger men (age < 60 y), but with an increased risk of high-grade cancer (13, 15), whereas one case-control study reported a reduced risk of both total and advanced cancer in association with obesity (23). The study of male health professionals, a large prospective study including more than 50,000 men and 2,896 prostate cancer cases, reported a 48% (95% CI: 0.33, 0.83) reduction in risk of prostate cancer among men younger than 60 y associated with BMI ≥ 30 (22 cases), relative to those with a BMI between 23 and 24.9 (13). In the same study, a 26% (95% CI: 0.45, 1.19) reduction in risk was seen among men with a family history of prostate cancer (13).
Similarly, a large nested case-control study of 1936 prostate cancer cases within the Prostate Cancer Prevention Trial Cohort showed that, compared with men with BMI < 25, obese men (BMI \geq 30) had an 18% decrease in the risk of low-grade prostate cancer (Gleason score \leq 7) but a 29% increase in the risk of high-grade prostate cancer (15). A recent case-control study of middle-aged men (median age: 58 y) with 753 cases and 703 controls also found a 23% reduction in risk (95% CI: 0.56, 1.06) associated with obesity (BMI > 29.1) (23). More recently, a large cohort study of 69 991 men with 5252 incident prostate cancer cases reported that BMI is associated with a 16% reduced risk of low-grade prostate cancer but a 22% increased risk of high-grade tumors (RR = 1.22) (16). Interestingly, as shown in Figure 1, the pooled relative risk for total prostate cancer was 1.03 (95% CI: 0.99, 1.07), whereas the overall RR was 0.85 for low-grade tumors and 1.25 for high-grade tumors.

Reasons for the inconsistent patterns related to high- and low-grade tumors, age at diagnosis, and family history of cancer are unclear. It has been hypothesized that differences in the pathogenesis and biology related to hereditary and sporadic tumors may account for some of the differential risk patterns. Hereditary cases are likely to be diagnosed at a younger age with a more aggressive form of prostate tumors. Thus, it is possible that hereditary tumors may require less environmental influence, whereas sporadic cases need additional factors, including higher levels of androgens, oxidative stress, and inflammation, to trigger cellular proliferation and tumor progression. These speculations, although preliminary and in need of confirmation, corroborate recent findings that higher serum testosterone concentrations are associated with an increased risk of low-grade prostate cancer but with a reduced risk of high-grade prostate cancer (29), which suggests etiological heterogeneity of prostate cancer related to both obesity and serum androgens.

**BMI and prostate cancer mortality**

In contrast with the confusing picture in prostate cancer incidence, conclusive evidence does exist that obesity is associated with prostate cancer aggressiveness, progression, and mortality (17, 26–28; Figure 1). The consistent positive association between prostate cancer mortality and obesity is due largely to the fact that mortality studies are generally larger (>3000 cases) and include mostly aggressive cases, thereby reducing the heterogeneity of cases; mortality is less affected by screening practices. Results from developing countries, where prostate cancer screening is less common and prostate cancers are usually diagnosed at a more advanced stage, have been more consistent and further support a possible role for obesity in prostate cancer mortality (30). Note that in the most recently published prospective study, Wright et al (17) reported no association of BMI with low-grade cancer but a positive association with fatal prostate cancer. The pooled RR for prostate cancer mortality associated with BMI was 1.25 (95% CI: 1.14, 1.38) (Figure 1). The positive findings in mortality studies, coupled with the mostly null results in studies of prostate cancer incidence, lend further support for the hypothesis that obesity may have a differential effect on different subtypes of prostate tumors (high- and low-grade).

**Early-adult BMI**

Most studies assessing the effect of obesity on prostate cancer have examined the role of usual adult BMI. In case-control studies, usual adult BMI represents BMI around the time of cancer diagnosis (median age of 68 y), whereas in prospective studies, BMI among subjects is captured in the subjects’ fifth or sixth decade of life, because most cohort members are recruited in this age range. Thus, usual adult BMI does not reflect BMI changes over time, nor does it reveal BMI in early adulthood, although some studies have shown positive correlations between BMI
measures at various ages. Although the mechanisms underlying the association between obesity and prostate cancer are unclear, it has been suggested that changes in serum concentrations of androgen and sex hormone–binding globulin may play a role. However, because it is uncertain at what age androgen is most relevant to prostate carcinogenesis, it is also unclear at what point in life obesity and its influence on androgen concentrations and metabolism have the greatest effect on the pathogenesis of prostate cancer. Some evidence exists that prostate cancer or its precursors, such as high-grade prostatic intraepithelial neoplasia or prostate inflammatory atrophy, can be detected in men as young as in their mid-20s, which suggests that BMI and androgen concentrations in early adulthood may also be relevant (31).

Four studies, including 2 cohort studies and 3 case-control studies, have examined the role of early adult BMI, with mostly null results. Two studies reported opposing significant results: a prospective study indicated that preadult obesity (at age 10 y) was associated with a 28% lower risk of advanced cancer (95% CI: 0.47, 1.10), whereas a case-control study of 1294 cases found an increased prostate cancer risk (17, 22; Figure 2). Currently, the data on preadult obesity are too sparse to yield any definitive conclusions. However, the hypothesis that the hormonal milieu in early life may affect subsequent prostate cancer risk is biologically plausible and needs to be investigated further.

**Abdominal obesity and prostate cancer**

Although intraabdominal fat makes up only 10% of total body fat, it is metabolically more active than subcutaneous or peripheral fat. Abdominal obesity is also more closely linked to insulin resistance and adverse outcomes, such as cardiovascular disease and diabetes. In epidemiologic studies, waist circumference and waist-to-hip ratio (WHR) are commonly used to define the extent of abdominal obesity, because waist size is not directly related to height. A waist circumference of >102 cm in men is defined as having excess abdominal fat, even if the man’s BMI is normal. Note that in older men, whose muscle is progressively lost with advancing age, BMI is a poor measure of body fat because it does not differentiate between fat and fat-free mass.

The recent meta-analysis by MacInnis and English (12) included 4 cohort studies and 5 case-control studies that assessed the role of central obesity in prostate cancer (18, 34–36). The overall risk estimate for waist circumference was 1.03 (95% CI: 0.97, 1.09) for prospective studies and 1.03 (95% CI: 0.98, 1.09) for case-control studies (Figure 3). A small study of 63 prostate cancer cases and 63 age-matched healthy control subjects that assessed body fat distribution by computed tomography scan showed that prostate cancer patients had a significantly higher abdominal fat area (37). The abdominal fat observed was mostly due to a higher amount of visceral fat and a significantly higher mean ratio of visceral to subcutaneous fat, with an odds ratio of 4.6 (95% CI: 2.6, 8.2) for high visceral fat, which suggests a potential role of abdominal obesity in prostate cancer (37). Although biologically, abdominal fat is metabolically more active and is more related to androgen metabolism, at present, the data are insufficient to draw a conclusion regarding the role of abdominal obesity in prostate cancer.
<table>
<thead>
<tr>
<th>First author, year, and reference</th>
<th>Study design</th>
<th>Population</th>
<th>Time period</th>
<th>Exposure</th>
<th>Covariates</th>
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<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Leptin (11 studies)</strong></td>
<td></td>
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<tr>
<td>Baillargeon, 2006 (25)</td>
<td>Nested C-C</td>
<td>US, Texas</td>
<td>2001–2005</td>
<td>Serum leptin</td>
<td>Age, race/ethnicity</td>
<td>For serum leptin: OR 0.77 (0.43, 1.37)</td>
<td>Null</td>
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<td></td>
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<td>125 prostate cancers, 125 controls</td>
<td>BML</td>
<td>BML, baseline PSA</td>
<td>T1 (reference)</td>
<td>T2.051 (0.19, 1.27)</td>
<td>T3.128 (0.57, 2.28)</td>
</tr>
<tr>
<td>Statin, 2001 (39)</td>
<td>Nested C-C</td>
<td>Sweden</td>
<td>1985–1999</td>
<td>Plasma leptin</td>
<td>BML, insulin, cholesterol, fasting and postload glucose, diastolic and systolic BP, smoking, snuffing, IGF-1, IGFBPs 1–3, testosterone, SHBG</td>
<td>Quantile Unadjusted RR (95% CI)</td>
<td>Positive for moderately elevated leptin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>149 prostate cancer cases, 298 controls</td>
<td>Mean age ~ 58.5 y</td>
<td>Mean follow-up ~ 6.5 y</td>
<td>Most cases had localized tumors with intermediate or high differentiation</td>
<td>Q2:2.1 (1.3, 4.1)</td>
<td>Q3:2.6 (1.4, 4.8)</td>
</tr>
<tr>
<td>Statin, 2003 (43)</td>
<td>C-C</td>
<td>Norway</td>
<td>Not given</td>
<td>Serum leptin</td>
<td>Testosterone, estradiol, SHBG</td>
<td>Quantile Adjusted RR (95% CI)</td>
<td>Null</td>
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<tr>
<td></td>
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<td>200 prostate cancer cases, 397 controls</td>
<td>Serum leptin</td>
<td>Serum leptin</td>
<td>Serum leptin positively correlated with age, year at diagnosis, BML</td>
<td>Q1:1.0 (reference)</td>
<td>Q2:1.0 (0.6, 1.7)</td>
</tr>
<tr>
<td>Haug, 2001 (36)</td>
<td>C-C</td>
<td>China</td>
<td>1993–1995</td>
<td>Serum leptin</td>
<td>Age, education, BMI, WHR, insulin, IGF-I</td>
<td>Tertiles (mg/L) OR (95% CI)</td>
<td>Null</td>
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<tr>
<td></td>
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<td>128 prostate cancer cases, 306 controls</td>
<td>Serum leptin</td>
<td>Serum leptin</td>
<td>Serum leptin</td>
<td>Low (1.50–2.90) 1.00 (reference)</td>
<td>Mid (3.01–4.00) 0.38 (0.18, 0.81)</td>
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<tr>
<td>Lagiou, 1998 (40)</td>
<td>C-C</td>
<td>Greece</td>
<td>1993–1994</td>
<td>Serum leptin</td>
<td>Age, height, BMI, education, estradiol, testosterone, dehydroepiandrosterone sulfate, SHBG, IGF-I</td>
<td>Per 4-ng/mL increment of leptin (~1 SD)</td>
<td>Null</td>
</tr>
<tr>
<td></td>
<td></td>
<td>43 prostate cancer patients, 41 BPH patients, 48 healthy controls</td>
<td>Serum leptin</td>
<td>Serum leptin</td>
<td>Serum leptin</td>
<td>For prostate cancer:</td>
<td>OR = 0.70 (0.32, 1.55), P = 0.38</td>
</tr>
<tr>
<td>Friedland, 2005 (42)</td>
<td>Case only</td>
<td>US, Maryland</td>
<td>1998–1999</td>
<td>Serum leptin</td>
<td>Serum leptin positively correlated with BMI (r = 0.0662, P &lt; 0.001). Higher leptin in men with T1c vs T2/T3 disease (mean: 7.4 ± 5.2 vs 5.8 ± 4.1 ng/mL, rank sum P = 0.03). No significant correlations between serum leptin and serum total or percent free PSA, biopsy or prostatectomy Gleason score, age, or height.</td>
<td>Serum leptin</td>
<td>Positive</td>
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<td>225 men treated with radical prostatectomy</td>
<td>Serum leptin</td>
<td>Serum leptin</td>
<td>Serum leptin</td>
<td>No association of serum leptin with pathological stage (P = 0.4).</td>
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<tr>
<td>Chang, 2001 (44)</td>
<td>Case only</td>
<td>US, Texas</td>
<td>1996–1998</td>
<td>Plasma leptin</td>
<td>Age, year at diagnosis, BMI</td>
<td>Overall OR = 2.35 (1.01, 5.44)</td>
<td>Positive</td>
</tr>
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<td></td>
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<td>199 white men (48 with tumors ≥0.5 cm vs 151 with tumors &gt;0.5 cm in volume or extraprostatic extension but no metastases)</td>
<td>Plasma leptin</td>
<td>Plasma leptin</td>
<td>Plasma leptin</td>
<td>For men with high leptin and high testosterone: OR = 9.73 (2.05, 46.24)</td>
<td>For men with high leptin and &gt;5% W” in height: OR = 3.67 (1.40, 9.63)</td>
</tr>
<tr>
<td>Saglam, 2005 (38)</td>
<td>Cross-sectional</td>
<td>Turkey</td>
<td>1999–2000</td>
<td>Serum leptin</td>
<td>Serum leptin</td>
<td>No significant differences in age, BMI, SHBG between groups. Significant difference in serum leptin concentrations between cancer vs controls and between cancer vs benign prostatic obstruction. Group Mean leptin (ng/mL)</td>
<td>Calcium 2.55 ± 12.50</td>
</tr>
<tr>
<td></td>
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<td>21 prostate cancer cases, 50 with benign prostatic obstruction, 50 healthy controls</td>
<td>Serum leptin</td>
<td>Serum leptin</td>
<td>Serum leptin</td>
<td>Benign 16.96 ± 6.27</td>
<td>Control 17.55 ± 7.20</td>
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<td></td>
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<td></td>
<td>Intercoation of plasma testosterone, SHBG, IGF-I, insulin, &amp; leptin</td>
<td>Age, case-control status</td>
<td>Correlations similar between cases and controls, so results reported for cases and controls combined.</td>
<td>Testosterone positively correlated with SHBG. Testosterone and SHBG negatively correlated with IGF-1, IGFBP-3, insulin, leptin, and BMI.</td>
</tr>
<tr>
<td>Kaaks, 2003 (41)</td>
<td>Cross-sectional</td>
<td>Sweden</td>
<td>149 prostate cancer cases, 298 controls. Most cases with small, high, or intermediate differentiated tumor; median PSA: 12 ng/mL. Time between blood collection and dx: 3.85 y (range: 1 mo to 10 y)</td>
<td>Not given</td>
<td>Intercoation of plasma testosterone, SHBG, IGF-I, insulin, &amp; leptin</td>
<td>Age, case-control status</td>
<td>Correlations similar between cases and controls, so results reported for cases and controls combined.</td>
</tr>
<tr>
<td>Genetic variant (2 studies)</td>
<td></td>
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<td>LEP gene locus ~ 2548 GA</td>
<td>Age, case-control status</td>
<td>Correlations similar between cases and controls, so results reported for cases and controls combined.</td>
<td>Testosterone positively correlated with SHBG. Testosterone and SHBG negatively correlated with IGF-1, IGFBP-3, insulin, leptin, and BMI.</td>
</tr>
<tr>
<td>Ribeiro, 2004 (45)</td>
<td>C-C</td>
<td>Portugal</td>
<td>1999–2002</td>
<td>LEP gene locus ~ 2548 GA</td>
<td>Age, case-control status</td>
<td>Genotype OR (95% CI)</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>141 prostate cancer cases, 118 controls</td>
<td>LEP gene locus</td>
<td>LEP gene locus</td>
<td>LEP gene locus</td>
<td>AG (vs GG) 2.93 (1.27, 6.75)</td>
<td>P for trend = 0.001</td>
</tr>
</tbody>
</table>

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TABLE 1 (Continued)

<table>
<thead>
<tr>
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</tr>
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<tbody>
<tr>
<td>Kote-Jarai, 2003 (46)</td>
<td>C-C</td>
<td>UK 271 prostate cancer cases aged &lt;50 y at dx, 277 controls</td>
<td>Not given</td>
<td>Lentin receptor (OBR) gene polymorphisms: Lys109Arg Glu223Arg</td>
<td>Genotype OR (95% CI): Lys109Arg 1.00 (reference) = 1.09 (1.48) = 1.36 (1.65, 2.85); Glu223Arg 1.00 (reference)</td>
<td>Null</td>
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<tr>
<td>Insulin or C-peptide (8 studies)</td>
<td>5 Serum studies</td>
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<tr>
<td>Giovannucci, 2004 (49)</td>
<td>Cohort</td>
<td>US 47,690 male health professionals aged 40–75 at baseline (1990–2010): 370 prostate cancer cases (299 aggressive prostate cancers)</td>
<td>1986–1998</td>
<td>C-peptide score (based on BMI, physical activity, and Western dietary pattern)</td>
<td>Age, race, alcohol intake, smoking history, height</td>
<td>Quotient Adjusted RR (95% CI) For total cancer: Q1 1.00 (reference) Q2 1.07 (0.95, 1.19) Q3 1.05 (0.94, 1.18) Q4 1.08 (0.97, 1.21)</td>
<td>Positive for Western-related cancers</td>
</tr>
<tr>
<td>Hubbard, 2004 (54)</td>
<td>Cohort</td>
<td>US 827 male prostate cancer patients</td>
<td>1958 to present</td>
<td>Fasting insulin, 2-h insulin, fasting glucose, HOMA</td>
<td>Fasting insulin Q1 1.00 Q2 0.91 (0.48, 1.75) Q3 1.20 (0.65, 2.25) Q4 0.71 (0.34, 1.54)</td>
<td>P for trend 0.56</td>
<td>Null for aggressive prostate cancer</td>
</tr>
<tr>
<td>Stattin, 2001 (39)</td>
<td>Nested C-C</td>
<td>Sweden 149 prostate cancer cases, 288 controls</td>
<td>1985–1999</td>
<td>Plasma insulin</td>
<td></td>
<td>Quotient Unadjusted RR (95% CI)</td>
<td>Null</td>
</tr>
<tr>
<td>Hammarsten, 2001 (50)</td>
<td>Case only</td>
<td>Sweden 320 prostate cancer cases (54 died from prostate cancer, 219 still alive during follow-up) Mean follow-up: 1233 d</td>
<td>1995–2003</td>
<td>Plasma insulin</td>
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<td>Genetic variant (3 studies)</td>
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<td>Neumann, 2005 (51)</td>
<td>C-C</td>
<td>US, Utah 199 prostate cancer cases, 267 controls</td>
<td>1992–1999</td>
<td>INS + +1127 Insulin Genes: BSJ G972R, BSJ G1079D</td>
<td>Age</td>
<td>IRS G972R GBR genes were associated with a significant 2.5 fold increase in risk of prostate cancer (95% CI: 1.5, 5.2; P = 0.0007) as well as higher grade and stage of prostate cancer.</td>
<td>Positive</td>
</tr>
<tr>
<td>Claey, 2005 (53)</td>
<td>C-C</td>
<td>US, Michigan Flint Men’s Health Study 124 prostate cancer cases, 342 controls African American men Ages 40–79 y</td>
<td>1996–2002</td>
<td>Ins Polymorphism</td>
<td>Age, BMI, diabetes</td>
<td>Overall CC vs (FT and TT): OR = 1.59 (0.93, 2.72) By BMI ≥ 30: OR = 1.67 (0.62, 4.51) &lt;30: OR = 1.75 (0.89, 3.45) By diabetes Yes: OR = 2.35 (0.78, 7.26) No: OR = 1.55 (0.82, 2.94) Pooled data with Ho et al (2003) CC vs (FT and TT): OR = 1.53 (1.01, 2.32)</td>
<td>Positive</td>
</tr>
</tbody>
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(Continued)
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Metabolic syndrome (6 studies)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Tuomima, 2007 (54)</td>
<td>Cohort</td>
<td>Finland</td>
<td>Helsinki Heart Study</td>
<td>Ages 40–58 yrs</td>
<td>175 prostate cancer cases, 46 controls</td>
<td>1981–1982</td>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td>Laukkanen, 2004 (57)</td>
<td>Cohort</td>
<td>Finland</td>
<td>Cohort</td>
<td>Finland</td>
<td></td>
<td>Follow-up through 1997</td>
<td></td>
</tr>
<tr>
<td>Lund Haheim, 2006 (56)</td>
<td>Cohort</td>
<td>US</td>
<td>6429 men</td>
<td>Ages 45–64 y</td>
<td>385 prostate cancer cases</td>
<td>1987–1989</td>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td>Bonivas, 2004 (58)</td>
<td>Metanalysis</td>
<td>US</td>
<td>14 studies</td>
<td>(9 cohort, 5 C-C)</td>
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<tr>
<td>Gong, 2006 (15)</td>
<td>Cohort</td>
<td>US</td>
<td>Prostate Cancer Prevention Trial</td>
<td>15 433 men, 15 prostate cancer cases, 8 322 controls</td>
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<td>Beebe-Dimmer, 2007 (35)</td>
<td>C-C</td>
<td>US, Michigan</td>
<td>Flint Men’s Health Study</td>
<td>Ages 40–79 yrs</td>
<td>African American men</td>
<td>1996–2002</td>
<td>Metabolic syndrome</td>
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<tr>
<td>Coker, 2004 (61)</td>
<td>C-C</td>
<td>US, South Carolina</td>
<td>15 407 prostate cancer cases, 472 prostate cancer cases, 359 controls</td>
<td>Ages 65–79 yrs</td>
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<td><strong>Diabetes (9 studies) - since 2002</strong></td>
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<tr>
<td>Beebe-Dimmer, 2007 (35)</td>
<td>C-C</td>
<td>US, Michigan</td>
<td>Flint Men’s Health Study</td>
<td>139 prostate cancer cases, 359 controls</td>
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<tr>
<td>Hammarsten, 2004 (50)</td>
<td>Cohort</td>
<td>Finland</td>
<td>15 433 men</td>
<td>Ages 40–79 yrs</td>
<td>African American men</td>
<td>1997–1999</td>
<td>Metabolic syndrome</td>
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<td>Beebe-Dimmer, 2007 (35)</td>
<td>C-C</td>
<td>US, Michigan</td>
<td>Flint Men’s Health Study</td>
<td>Ages 40–79 yrs</td>
<td>African American men</td>
<td>1997–1998</td>
<td>Metabolic syndrome</td>
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<td>Coker, 2004 (61)</td>
<td>C-C</td>
<td>US, South Carolina</td>
<td>15 407 prostate cancer cases, 472 prostate cancer cases, 359 controls</td>
<td>Ages 65–79 yrs</td>
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(Continued)
LEPTIN AND PROSTATE CANCER

Leptin, a cytokine produced by white adipose tissue, plays a critical role in the regulation of body weight by inhibiting food intake and stimulating energy expenditure. In addition, leptin influences cellular differentiation and progression in prostate cancer cells (38). Few epidemiologic studies have investigated the role of leptin in prostate cancer. Eight studies, including 2 prospective studies and 3 case-control studies, have examined the role of serum leptin (36, 38–44), whereas 5 studies have investigated the role of leptin in prostate cancer. Eight studies, including 2 prospective studies and 3 case-control studies, have examined the role of serum leptin (36, 38–44), whereas 5 studies have investigated the role of leptin in prostate cancer. Eight studies, including 2 prospective studies and 3 case-control studies, have examined the role of serum leptin (36, 38–44), whereas 5 studies have investigated the role of leptin in prostate cancer.

INSULIN RESISTANCE AND PROSTATE CANCER

Few studies have investigated the role of insulin or insulin resistance in prostate cancer, largely because the association between obesity and prostate cancer is inconsistent and most epidemiologic studies did not collect overnight fasting blood samples for the measurement of insulin. Five studies with different designs in different populations, including the United States, Sweden, and China, have examined the role of serum insulin or C-peptide in prostate cancer (Table 1 and Figure 5; 34, 35, 49, 50, 65). Of these, one prospective study measured serum C-peptide in 3270 prostate cancer cases (259 had aggressive prostate cancer) and found no association (RR = 1.10; 95% CI: 0.82, 1.47) (49). One small prospective study with 87 prostate cancer cases found no association of baseline glucose and insulin concentrations with subsequent prostate cancer risk (34). Two studies in Sweden, one a prospective study with 149 cases and 298 controls, reported null results (40), whereas a clinical survey of 320 cases in Sweden showed that higher insulin concentrations were associated with more aggressive tumors (50). A population-based case-control study of 128 cases and 306 controls in China, a low-risk population, reported a 2.6-fold risk of prostate cancer among those in the third (highest) tertile of serum insulin concentrations relative to men in the lowest tertile (36, 65). Overall, these data do not support a role of insulin resistance in prostate cancer.
insulin receptor substrate (IRS) genes, are more consistent and lend support to a plausible role for insulin resistance in prostate cancer etiology (Figure 5; 51–53). Of the 3 case-control studies that examined polymorphisms of the INS and IRS genes, one showed that the IRS G972 GR/RR genotypes were associated with a 2.8-fold risk of prostate cancer (95% CI: 1.5, 5.1; \( P = 0.0007 \)), with a much higher risk for high-grade tumors (odds ratio (OR) = 6.3; 95% CI: 2.3, 17.6 for Gleason \( \geq 8 \)) (51). The INS PstI CC genotype was associated with a 74% increased risk (95% CI: 0.99, 3.05) in a small case-control study conducted in New York (52). The same marker was associated with a 59% excess risk of prostate cancer (95% CI: 0.93, 2.72) in a study of 466 African American cases, with a stronger risk for diabetes; the pooled estimate for the INS PstI marker for these studies was 1.53

FIGURE 4. Leptin concentration and genetic variant and risk of prostate cancer. RR, relative risk.

FIGURE 5. Insulin concentrations and risk of prostate cancer. INS PstI CC, genotype of the insulin (INS) gene; IRS G972 GR/RR, genotypes of the insulin receptor substrate (IRS) gene.
These results suggest that variants in genes in the insulin signaling pathway may confer risk to prostate cancer, and this association warrants further investigation.

METABOLIC SYNDROME AND PROSTATE CANCER

Metabolic syndrome is an emerging hypothesis in the etiology of prostate cancer, although the evidence for this link is limited. Metabolic syndrome, also called insulin resistance syndrome, is defined as a constellation of metabolic abnormalities, including glucose intolerance (fasting plasma concentrations > 110 mg/dL), dyslipidemia (serum triacylglycerol concentration ≥ 150 mg/dL, serum HDL concentration < 40 mg/dL), hypertension (blood pressure ≥ 130/85 mm Hg), and obesity (a waist circumference of >102 cm). A recent community-based case-control study of African Americans reported a 90% excess risk of prostate cancer associated with metabolic syndrome (35). Of the 3 prospective studies that specifically addressed the role of metabolic syndrome in prostate cancer (55–57), one US study (6429 men and 385 cases) found an inverse association between metabolic syndrome and prostate cancer risk, with men having 3 adverse metabolic factors showing a 23% reduced risk (95% CI: 0.60, 0.98) (55; Table 1 and Figure 6). In addition, diabetes is included as one of the metabolic syndrome components; thus the observed reduced risk associated with metabolic syndrome may reflect, to a certain extent, an inverse association between diabetes and prostate cancer. Note that in this study, nondiabetic men with 2 of the traits of metabolic syndrome (having ≥3 factors defined as having metabolic syndrome) had a 37% significantly increased risk (95% CI: 1.01, 1.87), relative to those without any metabolic syndrome component, which suggests that the extent and duration of metabolic syndrome may influence the risk of prostate cancer differentially.

In contrast, 2 studies in Finland found a positive association between metabolic syndrome and prostate cancer, with one study of 507 prostate cancer cases reporting a 56% increased risk (P = 0.001) for men with 3 metabolic factors (56) and the other showing a 94% excess risk among those with metabolic syndrome (57). In addition, in a clinical survey of 299 prostate cancer patients, patients who died of prostate cancer were more obese (P = 0.062); had higher BMI (P = 0.003), waist measurement (P = 0.011), hip measurement (P = 0.051), and systolic blood pressure (P < 0.07); and had a faster rate of growth of benign prostate hyperplasia (P < 0.001) than did patients with T2 clinical prostate cancer (50).

Data on metabolic syndrome and prostate cancer are limited, and few studies have studied all 5 components of metabolic syndrome. It is unclear whether a change in one or 2 components can reflect the overall effect of metabolic syndrome. Thus, we conclude that although the metabolic syndrome hypothesis is highly plausible, currently, the epidemiologic evidence is insufficient to suggest a link between metabolic syndrome and prostate cancer.

DIABETES AND PROSTATE CANCER

Despite the strong association of diabetes with obesity and insulin resistance, diabetes has been consistently linked to a reduced risk of prostate cancer in several prospective and case-control studies, although the magnitude of the association is modest. In a 2004 meta-analysis of 14 studies, the pooled relative risk between diabetes and prostate cancer was 0.91 (95% CI: 0.86, 0.96) (58). Since the 2004 report, 6 additional studies have been published showing a reduced risk of prostate cancer associated with diabetes (59–64, 66; Table 1 and Figure 7).

Although on the surface the lower prostate cancer risk among men with diabetes appears to be in conflict with the hypothesis
that obesity and metabolic syndrome are associated with a higher risk of prostate cancer, a closer examination of the diabetes–prostate cancer association reveals additional support for the hypothesis that higher insulin concentrations and insulin resistance may increase the risk of prostate cancer. Diabetes is a complex disease, and insulin concentrations vary during its long natural history. Men with diabetes initially have higher concentrations of insulin as the result of insulin resistance but subsequently become insulin-deficient as a result of damaged pancreatic β-cells. The lower prostate cancer risk associated with long-term diabetes has been attributed, in part, to the lower serum concentrations of insulin and testosterone among men with diabetes (67). Indeed, in a large follow-up study of >5000 prostate cancer cases, risk of prostate cancer was slightly increased during the first 3 y after diagnosis of diabetes (RR = 1.23; 95% CI: 0.92, 1.65) but was reduced among men with diabetes for ≥4 y (RR = 0.63; 95% CI: 0.56, 0.71) (64). Further supporting this result is the finding from the US Physicians Study of >1000 cases of prostate cancer that men with long-term diabetes tend to have a lower risk of prostate cancer, in particular, the more aggressive form of prostate tumors (66).

Although the mechanisms underlying the link between diabetes and reduced prostate cancer risk are unclear, lower concentrations of insulin, testosterone, and insulin-like growth factor-I (IGF-I), as well as higher concentrations of estrogens, have been implicated. It is well established that obese men have lower concentrations of serum testosterone and sex hormone–binding globulin and higher concentrations of estrogen, which may be associated with lower risk of prostate cancer (29). In addition, insulin down-regulates IGF-binding protein 1, thus increasing bioavailable IGF-1. Higher concentrations of IGF-1 are associated with an increased risk of prostate cancer (29); thus, lower concentrations of insulin among men with long-term diabetes are associated with lower concentrations of free IGF-1 and reduced risk of prostate cancer.

Note that insulin concentrations per se may not sufficiently characterize the relation between diabetes and prostate cancer, because insulin sensitivity varies widely among individuals, and many patients who are insulin-resistant maintain their ability to secrete insulin (67). During the development of type 2 diabetes, β-cell function is progressively lost. At the time of diabetes diagnosis, a substantial amount, up to 50%, of β-cell function has already been lost. Thus, the duration and extent of diabetes and insulin action are more relevant in the pathogenesis of prostate cancer, although these factors are usually more difficult to measure in epidemiologic investigations. Large prospective studies that assess diabetes, insulin resistance, and sex hormones are needed to dissect the roles of these interrelated factors in prostate cancer.

MECHANISMS WHEREBY OBESITY AND METABOLIC SYNDROME MAY AFFECT PROSTATE CANCER RISK

Several mechanisms could explain the association of obesity and metabolic syndrome with prostate cancer risk, including the sex steroid hormone, insulin and IGF signaling, and inflammation pathways (Figure 8). Note that part of the speculative mechanisms presented in this figure, especially those related to the hypothesis that tumors become androgen-independent and can adapt to lower concentrations of testosterone, need confirmation in future studies.

The sex steroid pathway

The relation of prostate cancer with sex steroids and obesity is complex, and the underlying biological mechanisms are unclear. The current dogma regarding androgens and prostate cancer is that higher concentrations of androgens increase the risk of prostate cancer. Testosterone is metabolized intracellularly into dihydrotestosterone (DHT), and DHT then binds to the androgen receptor and its coactivators to form an intracellular complex that
then binds to the androgen response elements in the prostate gene to initiate a cascade of androgen signaling (68). Thus, intuitively, obesity may protect against prostate cancer, because obese men have modestly lower concentrations of serum testosterone, substantially lower concentrations of sex hormone–binding globulin, and higher concentrations of estrogens (69–71). However, more recent data have shown that higher serum concentrations of total testosterone are associated with a reduced risk (OR = 0.26; 95% CI: 0.10, 0.61) of high-grade (Gleason ≥ 7) prostate cancer but with an increased risk (OR = 1.91; 95% CI: 0.89, 4.07) of low-grade tumors (29) and that estradiol is associated with a decreased risk of nonaggressive cancer but not aggressive cancer. These data underscore the complex interrelations between obesity and serum sex steroids and their differential effect on prostate cancer but further support the differential effect of obesity on subtypes of prostate cancer.

The complex relations among these factors are shown in Figure 8. As shown, obese men have an increased risk of high-grade prostate cancer and a lower concentration of serum testosterone, which has been shown to be associated with increased risk of high-grade tumors (29). One possible explanation for the association between lower concentrations of serum testosterone and an excess of high-grade tumors is that a subset of the tumors may be more androgen-independent and thereby do not need high androgen concentrations for progression. Whether these tumors are the result of a stronger genetic predisposition or other adverse factors needs to be clarified in future studies. An alternative explanation is through the interaction with metabolic syndrome. It has been shown that men with low serum concentrations of testosterone are at an increased risk of developing metabolic syndrome. Whether low concentrations of serum testosterone reflect the insulin-resistant state in these patients and whether insulin alone, in the absence of high serum testosterone, is sufficient to trigger progression of prostate cancer to higher-grade tumors need to be clarified. Similarly, a possible explanation for the observation that lower testosterone concentrations are associated with a reduced risk of low-grade tumors may be that this subset of tumors is slow-growing and does need androgen stimulation for progression. These hypotheses are preliminary and need to be tested in future studies, but they do provide some support for the importance of etiologic heterogeneity in prostate cancer, which needs to be taken into account in future studies designed to clarify the role of androgens, obesity, and metabolic syndrome in prostate cancer.

### The IGF pathway

A potential mechanism for the link between metabolic syndrome and prostate cancer is through the IGF pathway. IGF-I plays an important role in cellular proliferation, differentiation, and reduction of apoptosis (72). Obesity is associated with increased free or bioavailable IGF-I (73), and several epidemiologic studies have reported a positive association between IGF-I and prostate cancer risk (72), although data from recent studies after the start of the prostate-specific antigen screening era are much weaker.

### The inflammation pathway

A plausible mechanism linking obesity and prostate cancer is chronic inflammation. Accumulating data support the hypothesis that chronic inflammation contributes to prostate carcinogenesis (73, 74). In addition, studies of genetic susceptibility have shown that variants of genes in the inflammation pathway, including *MSR1*, *TNF-α*, and *IL6*, are associated with a higher risk of prostate cancer (75–77).

It is now recognized that adipose tissue is an active organ that secretes a large number of proteins, including cytokines and hormone-like factors, such as leptin and adiponectin (75). It has been shown that obesity is associated with a state of low-grade
chronic inflammation, with infiltrating macrophages within adipose tissue and elevated concentrations of inflammatory cytokines, including tumor necrosis factor-α, interleukin-6, and C-reactive protein (78, 79). The subclinical inflammatory condition related to obesity promotes the production of proinflammatory factors involved in the pathogenesis of insulin resistance (80). Furthermore, in obesity, the proinflammatory effects of cytokines involve the nuclear factor-κB (NF-κB) and c-Jun N-terminal kinase (JNK) systems. Coincidentally, NF-κB is a strong inducer of anti-apoptotic gene activity (BCL-XL) and cell cycle genes (cyclin D1) (81). The net result is dependent on the state of activity of the JNKs. Nuclear localization of NF-κB is associated with prostate cancer (82). NF-κB is important in immune cell activation, and loss of NF-κB activity could alter immune surveillance for tumor cells (83). In a mouse model of colonic inflammation-associated cancer (84), loss of NF-κB activation within colonic epithelial cells led to decreased tumor incidence, whereas loss of NF-κB activation in myeloid cells decreased tumor size only. The hypothesis that inflammatory mediators could alter tumorigenesis is highly plausible, and the logical extension of this hypothesis is the speculation that increased NF-κB via select cytokine pathways could lead to cell survival, as has been shown for several tumor cell types.

In summary, the biological link between obesity and inflammation provides further support for the role of obesity in prostate cancer but adds additional complexity to the already confusing picture of the obesity-prostate cancer relation.

FUTURE DIRECTIONS
Worldwide, the prevalence of obesity is increasing, and in the United States, nearly two-thirds of adults are either overweight or obese. Given the rising epidemic of obesity and metabolic syndrome worldwide, especially in developing countries, and the potential links among obesity, androgen metabolism, diabetes, and inflammation, it is critical to understand better the complex relations between overall and abdominal obesity and prostate cancer risk and the role of chronic inflammation in obesity and the pathogenesis of prostate cancer.

Clearly, to dissect these interrelated factors, future prospective studies should be sufficiently large, with better assessment of overall and abdominal obesity and with biochemical measures, such as insulin concentrations, sex steroids, and IGFs, to clarify the complex interplays of these factors on prostate cancer risk. Etiologic heterogeneity should be considered. Further refinement of prostate cancer classification, using biomarkers and genetic markers, coupled with a clearer understanding of the cellular and molecular pathways involved, should prove illuminating. Factors such as grade, stage, and aggressiveness of tumors should be assessed and incorporated into the analysis. Methodologic studies are also needed to gain a better understanding of the determinants of these biomarkers, including insulin, leptin, adipokines, IGFs, sex steroids, and inflammatory mediators, and to provide biological data to help interpret the results.

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