Obesity, Adipokines, and Prostate Cancer in a Prospective Population-Based Study

Jacques Baillargeon,1,2 Elizabeth A. Platz,9 David P. Rose,1 Brad H. Pollock,1,2,3 Donna Paulaer Ankerst,10 Steven Haffner,4 Betsy Higgins,4 Anna Lokshin,11 Dean Troyer,5 Javier Hernandez,7 Steve Lynch,3 Robin J. Leach,2,6 and Ian M. Thompson4

1Center for Epidemiology and Biostatistics, Departments of Pediatrics, Medicine, Urology, Pathology, and Cellular and Structural Biology, University of Texas Health Science Center; 2Brooke Army Medical Center; 3Wilford Hall Medical Center, San Antonio, Texas; 4Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; 5Institute for Medical Informatics, Biometry and Epidemiology, University of Munich, Munich, Germany; and 6University of Pittsburgh Cancer Center, Pittsburgh, Pennsylvania

Abstract

Background: The purpose of this investigation was to examine the association of obesity and the adipokines leptin, adiponectin, and interleukin-6 (IL-6) with prostate cancer risk and aggressiveness.

Methods: One hundred twenty-five incident prostate cancer cases and 125 age-matched controls were sampled from among participants in the original San Antonio Center for Biomarkers of Risk of Prostate Cancer cohort study. The odds ratios (OR) of prostate cancer and high-grade disease (Gleason sum >7) associated with the WHO categories of body mass index (kg/m2) and with tertiles of serum concentrations of adiponectin, leptin, and IL-6 were estimated using multivariable conditional logistic regression models.

Results: Body mass index was not associated with either incident prostate cancer [obese versus normal; OR, 0.75; 95% confidence interval (95% CI), 0.38-1.48; Ptrend = 0.27] or high-grade versus low-grade disease (OR, 1.17; 95% CI, 0.39-3.52; Ptrend = 0.62). Moreover, none of the three adipokines was statistically significant associated with prostate cancer risk or high-grade disease, respectively: leptin (highest versus lowest tertile; OR, 0.77; 95% CI, 0.28-1.37; Ptrend = 0.57; OR, 1.20; 95% CI, 0.48-3.01; Ptrend = 0.85); adiponectin (OR, 0.87; 95% CI, 0.46-1.65; Ptrend = 0.24; OR, 1.93; 95% CI, 0.74-5.10; Ptrend = 0.85); IL-6 (OR, 0.84; 95% CI, 0.46-1.53; Ptrend = 0.98); OR, 0.84; 95% CI, 0.30-2.33; Ptrend = 0.17).

Conclusions: Findings from this nested case-control study of men routinely screened for prostate cancer and who had a high prevalence of overweight and obesity do not provide evidence to support that prediagnostic obesity or factors elaborated by fat cells strongly influence prostate cancer risk or aggressiveness. However, due to the small sample population, a small or modest effect of obesity and adipokines on these outcomes cannot be excluded.

Introduction

Obesity, a major public health problem in the United States (1, 2), is associated with several diseases, including cancer (1, 3). The association between obesity and prostate cancer, however, is complex, and studies have yielded inconsistent results (4-11). Investigations that have linked obesity with prostate cancer mortality, advanced stage, and higher Gleason score have produced more consistent findings (6-8), indicating that obesity may not necessarily increase the risk of the development of prostate cancer but may influence tumor growth and dissemination or differentiation state. One of the principal mechanisms whereby obesity may lead to such adverse outcomes is through the actions of adipokines, defined as biologically active polypeptide hormones produced by adipocytes. Three adipokines may have particular relevance to the study of prostate cancer risk and progression: leptin, adiponectin, and interleukin-6 (IL-6; ref. 12). Leptin promotes angiogenesis, influences the proliferation and migration of endothelial and epithelial cells (13-17), and has recently been identified as a novel growth factor that stimulates proliferation of androgen-independent prostate cancer cells in vitro (18). Although there is equivocal epidemiologic evidence implicating the role of leptin in the initiation of prostate cancer (19, 20), there are indications from some (12, 21, 22), but not all investigators (23), linking leptin to high-grade disease and more advanced tumors. Similarly, adiponectin affects both cellular proliferation and insulin sensitivity (12). Unlike leptin, however, it exhibits an inverse association with adiposity and body mass index (BMI; ref. 24). Recent studies indicate that circulating adiponectin levels is inversely associated with breast (25) and endometrial cancers (26) even after adjustment for BMI. Goktas et al. (27) reported that plasma adiponectin levels were inversely associated with both prostate cancer risk and disease stage in normal weight men. Moreover, Freedland et al. (28) reported that adiponectin was associated with high-grade prostate cancer but that this association was modified by BMI. Finally, IL-6 is an adipokine that regulates immune response and is also associated with cell growth, cell differentiation, and angiogenesis (24, 29, 30). Increased levels of IL-6 have been shown in prostate cancer cell lines and in human prostate cancer (31, 32). In prostate cancer patients, elevated circulating IL-6 levels have been associated with advanced disease stage, distant metastasis, metastasis-related morbidity, and decreased overall survival (29, 33-35). Additionally, findings from several studies indicate that IL-6 may play an important role as an autocrine growth factor in prostate cancer (32, 36, 37). In view of the increased rates of obesity in the United States, understanding the roles of obesity and adipokines in prostate carcinogenesis and progression holds particular clinical and public health relevance. The purpose of this investigation was to examine...
the association of obesity and the three adipokines, leptin, adiponectin, and IL-6, with prostate cancer risk and high-grade disease in the San Antonio Center for Biomarkers of Risk of Prostate Cancer (SABOR) study cohort. This cohort has a large proportion of overweight and obese men and provides an important opportunity to examine obesity-mediated prostate cancer.

Materials and Methods

Study Population. We identified incident prostate cancer cases and controls from among members of the original SABOR study cohort. SABOR is an ongoing prospective screening cohort of 4,500 men ages 25 to 90 years residing in San Antonio, Texas. This research represents a Clinical and Epidemiologic Center of the Early Detection Research Network and is supported by the National Cancer Institute. Recruitment of a multiethnic population-based sample was achieved using outreach clinics throughout metropolitan San Antonio. Healthy men without a history of prostate cancer were eligible for participation. All men who presented with prostate cancer at the initial evaluation were excluded. Participant enrollment into SABOR began in March 2001 with annual follow-up examinations. A concerted effort was made to oversample ethnic minorities and medically underserved populations. After completing the informed consent process, men completed a series of instruments (demographics, diet, quality of life, family history, ethnicity/race, and American Urological Association symptom score), provided biological samples, and underwent a directed physical examination, including a digital rectal examination and measurement of height, weight, and waist and hip circumferences. A blood specimen was collected on all SABOR participants at baseline. The clotted blood was centrifuged in a refrigerated centrifuge, and serum was stored at −70°C at the University of Texas Health Sciences Center at San Antonio (San Antonio, TX).

Approximately 1 month before their anniversary of their baseline visit, SABOR participants are contacted and given an appointment for their annual visit. At each annual visit, participants complete a brief survey of medical problems, including whether prostate cancer had been diagnosed since the time of the last visit, have their blood drawn, and undergo digital rectal examination. If the digital rectal examination is abnormal or prostate-specific antigen (PSA) exceeds 2.5 ng/mL, a prostate biopsy is recommended.

Prostate Cancer Cases and Controls. Irrespective of whether they were diagnosed based on the annual visit screening or between visits, all prostate cancer cases were reviewed by a central pathologist to confirm the diagnosis of adenocarcinoma and to determine Gleason sum. A total of 125 prostate cancer cases were diagnosed after enrollment in the cohort and through August 2005 (mean time from baseline to diagnosis, 1.43 ± 1.29 years). Of the cases, 84 were pathologic Gleason sum ≥6, 28 were Gleason sum 7, and 8 were Gleason sum ≥8. The cases were divided into high-grade (Gleason ≥7) and low-grade (Gleason ≤6) disease. The majority (67%) of cases were clinical stage T1 to T1c, 30% were clinical stage T2 to T3a, and only 3% were T3b or worse. For each case, one control was sampled from the cohort using incidence density sampling (38) to ensure that age-matched (+1 year) controls had accrued at least the same amount of follow-up time as the matched cases at their time of diagnosis.

Exposure Assessment. BMI (weight in kg/height in m²) was calculated from height and weight measured at initial visit and was categorized as follows: normal (BMI <25.0), overweight (BMI 25.0-29.9), and obese (BMI ≥30.0). These categories are consistent with those recommended by WHO (39). Serum concentrations of leptin, adiponectin, and IL-6 were measured in the sample collected at baseline using the LabMAP technology (Luminex, Austin, TX), which combines the principal of sandwich immunosassay with the fluorescent bead-based technology, allowing individual and multiplex analysis of up to 100 different analytes in a single microtiter well. This methodology is described in detail in the referenced article by Gorelik et al. (40).

Statistical Methods. All statistical analyses were done with the Statistical Analysis System version 8.0 (SAS Institute, Cary, NC). The distributions of demographic and clinical factors were compared between cases versus controls using McNemar’s test and the paired t test and between high-grade and low-grade cases using the χ² test and the t test. The distributions of the adipokine concentrations were right skewed; thus, nonparametric tests were used to compare the distributions between the cases and controls. Conditional logistic regression was used to estimate the odds ratio (OR) of prostate cancer for BMI, waist circumference, and the serum adipokines. We used unconditional logistic regression to estimate ORs of high-grade disease (Gleason >7) versus low-grade disease (Gleason ≤7). A series of indicator variables was entered into the model for categories of BMI and tertiles of waist circumference and serum concentration of each adipokine with cutoffs based on the distribution in the controls. We tested for trend by entering the median of each category or tertile as a continuous term into the model and then assessing the coefficient by the Wald test. In the multivariable model, we adjusted for race/ethnicity and age. Because we showed previously that obese men tend to have lower serum PSA and thus the likelihood of detection of an occult prostate cancer may be lower in obese men (41), we also adjusted for baseline PSA in the multivariable model. Because the adipokine concentrations are correlated, to determine the independent association for each adipokine with prostate cancer, in a subsequent analysis, the adipokines were mutually adjusted by including them simultaneously in the model. To determine whether the association of the adipokines with prostate cancer was independent of obesity, BMI was included in the model as a continuous variable in a subanalysis. All models were stratified by race/ethnicity (Hispanic/non-Hispanic), age at diagnosis (<60 years, ≥60 years), and PSA concentration at baseline (<2.0 ng/mL, ≥2.0 ng/mL) to assess effect modification. In addition, the models for the adipokines were stratified according to BMI (normal, overweight, and obese). With 125 case-control pairs, for a two-sided paired test with α = 0.05, we had 80% power to detect an OR of prostate cancer of ≥2.1 if the prevalence of exposure in the controls was 33% (e.g., obese versus not obese and top third versus not top third of adipokines).

Results

SABOR cases and controls were not statistically significantly different on demographic and clinical factors, although cases were slightly more likely to be African-American and controls were more likely to be Hispanic (Table 1). Men with high-grade versus low-grade disease were slightly younger but did not differ on race/ethnicity or family history.

Among the controls, BMI was weakly but statistically significantly inversely correlated with serum adiponectin (Spearman r = −0.21; P < 0.001) and more strongly and positively correlated with serum leptin (Spearman r = 0.60; P < 0.0001) but was not correlated with IL-6 (Spearman r = 0.03; P = 0.69).

Cases were slightly leaner on average than controls (Table 1). Compared with men with a reference range BMI, men who were obese had a nonstatistically significant lower odds of
prostate cancer, whereas overweight (25.0-29.9 kg/m²) men had a nonstatistically significant higher odds of prostate cancer both when taking into account age and after multivariable adjustment (Table 2). Men with a larger waist circumference possibly had a higher risk of high-grade versus low-grade disease but not total prostate cancer (Table 2).

Compared with controls, cases tended to have slightly lower concentrations of leptin and IL-6, but they did not differ on adiponectin concentration (Table 1). None of the adipokines was statistically significantly associated with prostate cancer, although the top tertile tended to be <1.0 for adiponectin and IL-6 in both the matched analysis and after multivariable adjustment (Table 3). Men with a higher adiponectin concentration seemed to have a higher risk of high-grade disease even after multivariable adjustment, although the trend was not statistically significant; leptin and IL-6 were not associated with high-grade disease.

Because adiposity may influence prostate cancer via mechanisms other than adipokines, we additionally adjusted for BMI in the multivariable model. Compared with the bottom tertile, men in the top tertile of adiponectin had a lower odds of prostate cancer and men in the top tertile of leptin had a higher odds of prostate cancer, although the trends were not statistically significant. Our evaluation of stratified models as well as interaction terms indicated that there was no effect modification by age, race/ethnicity, BMI, or baseline PSA value.

### Discussion

The current study does not provide evidence for a strong influence of BMI on prostate cancer risk or aggressiveness. Our findings are in contrast to those of several previous investigators that have linked obesity with increased mortality, advanced disease stage, higher Gleason grade (6-8), and with overall prostate cancer incidence (7, 9, 10). Prospective studies reporting an increased risk of prostate cancer among obese

| Table 1. Baseline demographic, clinical, and serum adipokines concentrations, cases versus controls, and high-grade versus low-grade disease from the SABOR cohort |
|----------------------------------|-----------------|----------------|-----------------|----------------|
|                                  | Cases (n = 125) | Controls (n = 125) | P               | High grade (n = 40) | Low grade (n = 85) | P               |
| Mean age ± SD (y)                | 63.5 ± 7.4      | 63.2 ± 7.6       | Matched         | 61.8 ± 7.1       | 63.7 ± 7.7       | 0.07 |
| Race/ethnicity (%)              |                |                 |                 |                 |                 |     |
| Non-Hispanic Caucasian          | 56.8            | 69.1            |                 | 56.3            | 56.1            | 0.86 |
| Hispanic Caucasian              | 26.4            | 19.1            |                 | 27.6            | 24.4            |     |
| African American                | 16.8            | 11.8            | 0.14            | 16.1            | 19.5            |     |
| Family history                  | Yes             | 30.4            | 26.0            | 35.9            | 26.2            |     |
|                                | No              | 69.6            | 74.0            | 64.1            | 73.8            | 0.27 |
| BMI (%)                         |                 |                 |                 |                 |                 |     |
| Normal (≤25 kg/m²)              | 16.9            | 17.5            |                 | 18.4            | 15.0            | 0.88 |
| Overweight (25.0-29.9 kg/m²)    | 50.0            | 38.1            | 0.12            | 49.4            | 50.0            |     |
| Obese (≥30 kg/m²)               | 33.1            | 44.4            | 0.08            | 32.2            | 35.0            |     |
| Mean BMI ± SD (kg/m²)           | 28.4 ± 4.1      | 29.4 ± 4.9      | 0.08            | 28.5 ± 4.5      | 28.1 ± 3.9      | 0.07 |
| Mean waist circumference ± SD (cm) | 101.8 ± 12.7 | 103.9 ± 12.6   | 0.08            | 102.1 ± 12.2    | 100.4 ± 12.9    | 0.07 |
| Serum adiponectin (µg/mL)       |                 |                 |                 |                 |                 |     |
| Mean ± SD                       | 17.9 ± 10.6     | 19.9 ± 13.2     | 0.20            | 19.8 ± 12.4     | 17.1 ± 4.4      | 0.19 |
| Median (interquartile range)    | 15.9 (11.2-22.4)| 15.84 (12.2-26.4)| 0.27         | 15.9 (12.4-23.2)| 15.9 (11.0-20.0)|     |
| Serum leptin (pg/mL)            |                 |                 |                 |                 |                 |     |
| Mean ± SD                       | 8.62 ± 7.4      | 11.1 ± 11.7     | 0.09            | 9.6 ± 9.4       | 8.2 ± 6.2       | 0.32 |
| Median (interquartile range)    | 6.3 (3.2-12.6)  | 7.6 (4.2-14.3)  | 0.11            | 6.6 (1.9-14.9)  | 5.9 (3.3-12.3)  | 0.34 |
| Serum IL-6 (pg/mL)              |                 |                 |                 |                 |                 |     |
| Mean ± SD                       | 70.9 ± 128.6    | 107.8 ± 180.5   | 0.07            | 46.2 ± 62.9     | 82.5 ± 68.7     | 0.06 |
| Median (interquartile range)    | 14.5 (1.5-182.7)| 19.6 (3.3-106.5)| 0.11            | 15.4 (3.7-52.6) | 12.1 (1.2-113.8)| 0.09 |

| Table 2. Prostate cancer and high-grade disease ORs by BMI and waist circumference from the SABOR cohort |
|---------------------------------|-----------------|-----------------|----------------|
| **BMI**                         | Prostate cancer, OR* (95% CI) | P_trend | High-grade disease, OR † (95% CI) | P_trend |
| Matched/age-adjusted analysis  |                               |        |                               |        |
| Normal (<25 kg/m²)              | 1.00 (referent)              |        | 1.00 (referent)               |        |
| Overweight (25.0-29.9 kg/m²)    | 1.38 (0.68-2.76)             | 0.27   | 1.12 (0.40-3.18)              | 0.62   |
| Obese (≥30 kg/m²)               | 0.75 (0.38-1.48)             |        | 1.17 (0.39-3.52)              |        |
| Multivariable adjusted         |                               |        |                               |        |
| Normal                         | 1.00 (referent)              |        | 1.00 (referent)               |        |
| Overweight                     | 1.45 (0.70-2.79)             |        | 1.29 (0.41-4.09)              |        |
| Obese                          | 0.72 (0.36-1.47)             | 0.22   | 1.07 (0.32-3.66)              | 0.70   |
| Waist circumference          |                               |        |                               |        |
| Matched/age-adjusted analysis  |                               |        |                               |        |
| Tertile 1                      | 1.00 (referent)              |        | 1.00 (referent)               |        |
| Tertile 2                      | 1.00 (0.54-1.84)             |        | 1.29 (0.48-3.43)              |        |
| Tertile 3                      | 0.56 (0.30-1.03)             |        | 2.00 (0.74-5.41)              | 0.17   |
| Multivariable adjusted        |                               |        |                               |        |
| Tertile 1                      | 1.00 (referent)              |        | 1.00 (referent)               |        |
| Tertile 2                      | 1.09 (0.51-2.36)             |        | 1.14 (0.41-3.15)              |        |
| Tertile 3                      | 0.56 (0.24-1.27)             | 0.19   | 1.71 (0.53-4.63)              | 0.29   |

*Estimated from conditional logistic regression models that took into account the matching factor age and adjusted for race/ethnicity.
† Compared with low-grade prostate cancer and estimated from unconditional logistic regression models adjusting for age and race/ethnicity.

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men include an 18-year study of 134,000 Swedish construction workers by Andersson et al. (42) and study by Schuurman et al. (5) of 58,779 men enrolled in the Netherlands cohort study. Other such prospective studies, however, report no association (43, 44). In view of previous reports that androgen-mediated reductions in PSA among overweight men may result in underascertainment of prostate cancer incidence in heavier men (41), we examined whether adjusting for the influence of PSA would increase the association between BMI and prostate cancer. Our results indicate, however, that the lack of association between both BMI and waist circumference with prostate cancer persisted even after multivariable adjustment that included PSA.

Investigations that have linked obesity with prostate cancer mortality, advanced stage, and higher Gleason grade (6-8, 45) have produced more consistent results. In view of this, it is not clear why a similar effect was not seen in our study. Because the present study was limited to 125 cases of prostate cancer, it is noteworthy that men classified in the highest tertile of waist circumference exhibited a decreased risk of prostate cancer but an increased risk of poorly differentiated tumors (46).

Given the lack of association between BMI and either incident prostate cancer or high-grade disease, we did not assess the extent to which the adipokines mediated BMI and disease risk. Instead, we examined the independent effects of all three adipokines (leptin, adiponectin, and IL-6) on each of the prostate cancer outcomes as well as the extent to which each of these effects was modified by BMI. Our findings show that none of the three adipokines under study was strongly associated with either of the two prostate cancer outcomes. Moreover, neither adjustment for nor stratification by BMI altered this lack of association in any of the evaluated statistical models. The absence of an association or trend for the models assessing adiponectin and leptin with high-grade disease is particularly surprising in view of recent epidemiologic studies (21, 22, 27).

In view of the short mean time between blood draw and diagnosis of prostate cancer (1.43 years) in this study relative to the time course of prostate carcinogenesis, it is likely that most of the men who became prostate cancer cases during the study period had extant yet undetected tumors at study entry. Whether occult disease that was PSA detected subsequently would influence circulating concentrations of adipokines is unknown.

All participants of the SABOR cohort, from which our sample of cases and controls was drawn, were screened at study entry and then annually using PSA, digital rectal examination, and prostate biopsy as indicated. Consequently, our study sample may be less representative of previous clinical and population-based studies but more reflective of the modern U.S. male population, in which consistent and rigorous screening has become common. The resulting low-stage variation exhibited by this study cohort offers an important opportunity to assess how obesity and associated adipokines were related to disease grade, independent of stage. It will be important for future studies to further examine the roles of obesity and adipokines in prostate carcinogenesis and disease progression in similar well-screened study samples.

### Table 3. Prostate cancer and high-grade disease ORs by serum adipokines tertiles from the SABOR cohort

<table>
<thead>
<tr>
<th>Adiponectin tertile</th>
<th>Matched/age-adjusted analysis</th>
<th>Multivariable adjusted</th>
<th>Matched/age-adjusted analysis</th>
<th>Multivariable adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tertile 1</td>
<td>1.00 (referent)</td>
<td>1.00 (referent)</td>
<td>1.00 (referent)</td>
<td>1.00 (referent)</td>
</tr>
<tr>
<td>Tertile 2</td>
<td>0.83 (0.43-1.58)</td>
<td>0.57 (0.30-0.97)</td>
<td>1.24 (0.44-3.50)</td>
<td>1.20 (0.48-3.01)</td>
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<tr>
<td>Tertile 3</td>
<td>0.87 (0.46-1.65)</td>
<td>0.77 (0.43-1.37)</td>
<td>0.51 (0.19-1.27)</td>
<td>1.28 (0.57-2.88)</td>
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</tr>
<tr>
<td>Leptin tertile</td>
<td>Matched/age-adjusted analysis</td>
<td>Multivariable adjusted</td>
<td>Matched/age-adjusted analysis</td>
<td>Multivariable adjusted</td>
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<tr>
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<td>1.00 (referent)</td>
<td>1.00 (referent)</td>
<td>1.00 (referent)</td>
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<tr>
<td>Tertile 2</td>
<td>0.50 (0.26-0.97)</td>
<td>0.77 (0.43-1.37)</td>
<td>0.51 (0.19-1.27)</td>
<td>1.28 (0.57-2.88)</td>
</tr>
<tr>
<td>Tertile 3</td>
<td>0.84 (0.46-1.53)</td>
<td>0.84 (0.30-2.33)</td>
<td>1.35 (0.52-3.52)</td>
<td>1.00 (referent)</td>
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<tr>
<td>IL-6 tertile</td>
<td>Matched/age-adjusted analysis</td>
<td>Multivariable adjusted</td>
<td>Matched/age-adjusted analysis</td>
<td>Multivariable adjusted</td>
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<tr>
<td>Tertile 1</td>
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<td>1.00 (referent)</td>
<td>1.00 (referent)</td>
<td>1.00 (referent)</td>
</tr>
<tr>
<td>Tertile 2</td>
<td>1.09 (0.61-1.93)</td>
<td>0.84 (0.46-1.53)</td>
<td>1.63 (0.75-3.65)</td>
<td>0.73 (0.42-1.26)</td>
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<tr>
<td>Tertile 3</td>
<td>0.84 (0.46-1.53)</td>
<td>0.84 (0.30-2.33)</td>
<td>0.87 (0.29-2.47)</td>
<td>1.00 (referent)</td>
</tr>
</tbody>
</table>

*Estimated from conditional logistic regression models that took into account the matching factor age and adjusted for race/ethnicity.

*Compared with low-grade prostate cancer and estimated from unconditional logistic regression models adjusting for age and race/ethnicity.
References


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