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EPIDEMIOLOGIC DETERMINANTS OF CLINICALLY RELEVANT PROSTATE CANCER

Margaret R. SPITZ[1]*, Sara S. STROM[1], Yuko YAMAMURA[1], Patricia TRONCOSO[2], Richard J. BABAIAN[3], Peter T. SCARDINO[4], Thomas WHEELER[4], Christopher I. AMOS[1], Andrew VON ESCHENBACH[3] and Jacob KAGAN[5]

[1]*Department of Epidemiology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA*
[2]*Department of Pathology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA*
[3]*Department of Urology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA*
[4]*Scott Department of Urology, Baylor College of Medicine, Houston, Texas, USA*
[5]*Department of Laboratory Medicine, The University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA*

While tumor volume and Gleason scores are the best available prognostic indicators for prostate cancer, contemporary predictive methods are unable to identify which men with Gleason scores of 7 have clinically insignificant tumors that will not progress and which men will develop highly aggressive prostate cancer. Our objective was to evaluate potential environmental determinants of significant prostate cancer. Subjects were patients identified from a university-based hospital and tertiary cancer center who had undergone radical prostatectomy for prostate cancer. Cases were 103 patients whose tumor volumes were ≤0.5 ml. The comparison group was comprised of 225 men with larger-volume disease or with histologic evidence of extracapsular extension but without lymph node involvement. The matching criteria were ethnicity, age at diagnosis (±5 years), and date of diagnosis (±1 year). Epidemiologic data, current weight, and height were obtained. The comparison group was significantly more likely than cases to be current smokers (7.6% *vs.* 3.9%) and to report more pack-years smoked (30.1 *vs.* 23.0 years, $p = 0.06$). Cases tended to weigh less (85.2 *vs.* 87.1 kg, $p = 0.1$) and have lower body mass indices (26.8 *vs.* 27.6, $p = 0.07$). A similar trend was evident for weight at age 40 (79 *vs.* 81 kg). Cases reported a mean weight gain of 4.9 kg compared with 6.6 kg in the comparison subjects ($p = 0.05$) between the ages of 25 and 40. There was no significant difference in weight gain from age 40 to current age. Cases were more likely to report having prostate cancer screening (90% *vs.* 80%, $p = 0.02$). Cases with Gleason scores ≤7 (3 + 4, with 3 being the dominant grade) were younger at diagnosis than those with scores of 7 (4 + 3, with 4 being the dominant grade), were more likely (93%) to have had prostate screening, were less likely to be current smokers (4%), reported the fewest pack-years smoked (21.5 *vs.* 28.6 years for high-score cases and 30.1 for comparison subjects), and had the lowest average weight gain from ages 25 to 40 (4.62 vs. 6.31 kg for high-score cases). Weight gain in early adulthood and smoking thus appear to be important predictors of virulent prostate cancer. Our data also suggest that prior screening is associated with diagnosis of lower-volume and lower-score disease. *Int. J. Cancer (Pred. Oncol.)* 89:259–264, 2000.
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There is considerable biologic heterogeneity in the presentation and outcome of prostate cancer. At one extreme is low-grade, small-volume disease, which is usually not detected; patients with this type of disease have prolonged asymptomatic survival and eventually die of unrelated causes. At the other extreme is rapidly progressive and fatal prostate cancer (Sakr, 1998). Conventional prognostic factors cannot predict biologic activity. McNeal (1992) reported that the most important prognostic parameter for adverse clinical outcome is tumor volume. Stamey *et al.* (1999) suggested that the combination of volume, Gleason score, and clinical stage is a more accurate predictor of disease outcome than tumor volume. Gleason scores >7 have been documented to be adverse prognostic predictors. However, patients with Gleason scores of 7 have a less predictable outcome. Tefilli *et al.* (1999) recommended that patients with a Gleason score of 7 be considered a specific prognostic category. Stamey *et al.* (1999) demonstrated that the Stanford modified Gleason scale of 4/5 (% Gleason grade 4/5) was independently associated with cancer progression, as defined by rising prostate-specific antigen (PSA) levels.

The rapid progression of prostate cancer may be due to genetic changes, stromal interactions, and/or environmental factors. The critical gap in prostate cancer epidemiology is the elucidation of which environmental factors determine the biologic behavior of virulent cancer. Thus, the purpose of our study was to evaluate potential determinants of prostate cancer progression.

We used tumor volume and pathologic stage to distinguish 2 groups of men with prostate cancer, to construct a study comparing a group of men with low-volume prostate cancer (cases) and an age- and ethnicity-matched group of men with clinically relevant prostate cancer (comparisons). These 2 groups were characterized by construction of comprehensive epidemiologic profiles, and cases were further stratified by Gleason score to identify epidemiologic determinants of progression to clinical prostate cancer.

MATERIAL AND METHODS

All study subjects had undergone radical prostatectomy for prostate cancer. Cases were defined as patients whose tumor volumes were ≤0.5 ml according to a standard protocol previously described (Babaian *et al.*, 1995). The comparison group was composed of patients who had organ-confined tumors with a total tumor volume >0.5 ml or tumors that exhibited extracapsular extension but without local or distant metastases. The matching criteria for selection of comparison subjects were ethnicity, age at diagnosis (±5 years), and date of diagnosis (±1 year). Gleason scores were not included as a selection criterion. Patients had reported no prior malignancies and had had no treatment other than total prostatectomy for prostate cancer.

Patients were identified by urologists (RJB and PTS) and pathologists (PT and TW) at The University of Texas M.D. Anderson Cancer Center and Baylor College of Medicine. A pathologist (PT or TW) confirmed the Gleason scores for all cases. All patients were diagnosed between January 1990 and November 1998, and interviews were conducted between February 1996 and December 1998. After informed consent was obtained, a structured interview of approximately 30 min was conducted by trained interviewers. Data were

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Dr. Scardino's current address is: Department of Surgery, Urology Service, Memorial-Sloan Kettering Cancer Center, New York, NY, USA.

*Correspondence to: Department of Epidemiology, Box 189, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, USA. Fax: +713-792-0807. E-mail: mspitz@mdanderson.org

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TABLE I – DISTRIBUTION OF SELECT CHARACTERISTICS BETWEEN CASES AND COMPARISON SUBJECTS

	Cases (n = 103)	Comparison subjects (n = 225)	*p* value
Mean age (years ± SD)	61.5±6.7	61.6±6.4	0.86
Mean educational attainment (years ± SD)	16.3±2.6	15.0±3.1	<0.001
Marital status			
Married	99 (96.1%)	200 (88.9%)	0.03
Not married	4 (3.9%)	25 (11.1%)	
Prior vasectomy			
Yes	34 (33.0%)	63 (28.0%)	0.40
No	69 (67.0%)	161 (71.6%)	
Family history of prostate cancer			
Yes	21 (20.4%)	49 (21.8%)	0.80
No	82 (79.6%)	176 (78.2%)	
Alcohol consumption			
Current	73 (70.9%)	151 (67.1%)	0.85
Former	12 (11.6%)	39 (17.3%)	0.24
Never	18 (17.5%)	35 (15.6%)	
Smoking status			
Current	4 (3.9%)	17 (7.6%)	0.15
Former	63 (61.2%)	142 (63.1%)	0.42
Never	36 (34.9%)	66 (29.3%)	
Mean pack-years smoked	23.0 ± 22.8	30.1 ± 27.8	0.06
Previous screening history			
Yes	93 (90.3%)	179 (79.6%)	0.02
No	10 (9.7%)	46 (20.4%)	

TABLE II – DISTRIBUTION OF ANTHROPOMETRIC VARIABLES BETWEEN CASES AND COMPARISON SUBJECTS

	Cases (n = 103)	Comparison subjects (n = 225)	*t*-test *p* value
Mean height (cm ± SD)	177.3± 6.2	177.2± 6.5	0.96
Mean current weight (kg ± SD)	85.2±11.6	87.1±12.6	0.10
Mean current BMI (± SD)	26.8± 3.2	27.6± 3.5	0.07
Mean weight at age 25 (kg ± SD)	74.1± 9.9	74.2±11.5	0.90
Mean BMI at age 25 (± SD)	23.6± 2.9	23.6± 3.2	0.91
Mean weight at age 40 (kg ± SD)	79.1±11.3	80.8±11.5	0.20
Mean BMI at age 40 (± SD)	25.1± 3.0	25.7± 3.0	0.12
Mean weight change from age 25 to 40 (kg ± SD)	4.9± 7.8	6.6± 7.1	0.05
Mean weight change from age 40 to current age (kg ± SD)	5.4± 7.8	5.8± 9.4	0.70

collected on sociodemographic characteristics, recent and prior tobacco and alcohol use, prostate cancer screening history, other lifestyle habits, and family history of cancer. Men were asked to recall their weight at ages 25 and 40. Current weight and height measurements were recorded by the interviewers at the time of the interview.

Data for cases and comparison subjects were compared to evaluate potential risk factors for higher-volume disease. A paired *t*-test was used to compare means for continuous variables, and χ^2 tests of independence were used for categorical variables. Statistical analysis was performed using the SPSS (Chicago, IL) software program with 0.05 as the 2-sided statistical significance level for all tests. "Current smokers" were defined as individuals who had smoked >100 cigarettes in their lifetimes and were still smoking or had quit <1 year before diagnosis. "Former smokers" were defined as ever-smokers who had quit at least 1 year before their cancer diagnosis. Pack-years were calculated by multiplying the average number of packs of cigarettes smoked per day and the number of years smoked. Patients were considered to have a positive family history of prostate cancer if they reported having at least 1 affected first-degree relative with prostate cancer. Body mass index (BMI) was computed according to the formula weight (kg)/height $(m)^2$. Univariate odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using these variables. Based on these results, we constructed a conditional logistic regression model that allowed us to assess the simultaneous effects of multiple potentially confounding exposure factors. The Stata computer package was used to calculate maximum-likelihood estimates.

Secondary analyses were also performed. The combined Gleason score was based on the sum of the 2 most prevalent grades and categorized as low [combined score ≤7 (3 + 4, with 3 being the dominant grade)] and high [combined score >7 (4 + 3, with 4 being the dominant grade)] scores to examine potential confounding resulting from the Gleason score.

RESULTS

Of the 125 patients who met the study eligibility criteria as cases and for whom we had accurate addresses, 107 (86%) agreed to participate. The participation rates for cases were similar for the 2 institutions (81% for patients from Baylor College of Medicine and 89% for patients from M.-D. Anderson Cancer Center). Of these 107 cases with low-volume disease, 41 were from Baylor College of Medicine and 66 from M.-D. Anderson Cancer Center. Comparison group participation was slightly higher, with 95% of eligible comparison group patients participating. Because there were few cases of other ethnic groups, only the 103 Caucasians were included in these analyses. The comparison group was derived from the M.-D. Anderson Cancer Center patient population and comprised 225 patients with tumors >0.5 ml and/or extracapsular extension, who were individually matched to cases by age, ethnicity, and year of diagnosis. Because of the limited number of patients available with low-volume disease, we used a variable matching ratio to enhance the power of the study.

TABLE III – DISTRIBUTION OF SELECT VARIABLES BY GLEASON SCORE

Variable	Cases		Comparison subjects (n = 225)
	Low score[1] (n = 83)	High score[2] (n = 20)	
Prior screening	92.8%	80.0%	79.6%
Current smoker	3.6%	5.0%	7.6%
Packs per day smoked (± SD)	1.1± 0.8	1.1± 0.7	1.2± 0.8
Years smoked (± SD)	18.2±11.1	23.6±14.9	24.0±12.5
Pack-years smoked (± SD)	21.5±21.4	28.6±27.4	30.1±27.8
Mean height (cm ± SD)	176.8± 5.9	179.2± 7.1	177.2± 6.5
Mean weight (kg ± SD)	85.9±12.1	82.2± 8.9	87.1±12.6
Mean current BMI (± SD)	27.2± 3.3	25.5± 2.5	27.6± 3.4
Mean weight at age 40 (kg ± SD)	79.3±11.8	78.4± 9.1	80.8±11.5
Mean BMI at age 40 (± SD)	25.3± 3.2	24.2± 2.2	25.7± 3.0
Mean weight at age 25 (kg ± SD)	74.5±10.2	72.1± 8.8	74.2±11.5
Mean BMI at age 25 (± SD)	23.8± 2.9	22.3± 2.6	23.6± 3.2
Mean weight change from age 25 to 40 (kg ± SD)	4.6± 7.8	6.3± 7.6	6.6± 7.1
Mean weight change from age 40 to current age (kg ± SD)	5.8± 7.9	3.8± 7.2	5.8± 9.4
Mean weight change from age 25 to current age (kg ± SD)	10.4±10.4	10.1±11.4	12.4±11.8
Mean Gleason score	6.0	7.1	7.3
Mean age (years ± SD)	61.1± 6.5	63.1± 7.1	61.6± 6.4

[1]Low score, combined Gleason score ≤7 (3 + 4).–[2]High score, combined Gleason score of 7 (4 + 3).

Table I summarizes the univariate distribution by case–comparison status of select sociodemographic variables. Reflecting the study design, the 2 groups of men were well matched on age. There were statistically significant differences between the 2 groups in educational attainment (16.3 years for cases *vs.* 15.0 years for comparisons, $p < 0.001$). Cases were also significantly more likely than the comparison group to be married (96.1% *vs.* 88.9%, respectively; $p = 0.03$). There were no statistically significant differences in vasectomy, self-reported history of prostate cancer in a first-degree relative (20.4% of cases reported such a history), or alcohol consumption or smoking status at diagnosis. However, comparison subjects were more likely than cases to be current smokers (7.6% *vs.* 3.9%, respectively) and to report more pack-years of exposure (30.1 *vs.* 23.0 years, respectively; $p = 0.06$).

The 2 groups of men were of similar mean height (177 cm) (Table II), though cases tended to weigh less (85.2 *vs.* 87.1 kg, respectively; $p = 0.1$). Therefore, their current BMIs also differed (26.8 *vs.* 27.6, respectively; $p = 0.07$). A similar but not statistically significant trend was evident for weight at age 40 (79.1 kg for cases *vs.* 80.8 kg for controls). However, there were no differences in reported weight at age 25. When subjects were grouped into quartiles of current BMI according to the distribution of cases, the adjusted OR (95% CI) values for the highest quartile of BMI were 1.74 (0.82–3.69) for current BMI in cases *vs.* comparisons, 1.88 (0.88–4.06) for BMI at age 40, and 1.09 (0.55, 2.17) for BMI at age 25 (data not shown). Weight change from age 25 to age 40 therefore appeared to be a significant predictor of risk (Table II). Cases reported a mean weight gain of 4.9 kg compared with 6.6 kg ($p = 0.05$). There was no significant difference in weight gain from age 40 to current age.

We also compared the screening histories of the 2 groups of men. Predictably, cases were more likely than comparison subjects to have had prostate cancer screening (90.3% *vs.* 79.6%, $p = 0.02$), especially PSA testing (Table I). Thirty-five (34%) cases compared with 23% of the comparisons reported that they had symptoms such as frequency or nocturia before their diagnoses.

Because of the important predictive value of Gleason scores, we re-analyzed the cases by Gleason score (Table III). Eighty-three (81%) cases had Gleason scores ≤7 (3 + 4), with 3 being the dominant grade; these cases were classified as low-volume, low-score. The other 20 cases (referred to as low-volume, high-score) had Gleason scores of 7, with 4 being the dominant grade, except for 1 patient with a tumor classified as Gleason 8. Among the comparison group, only 90 (40.0%) had scores of ≤7 (3 + 4).

TABLE IV – RISK ESTIMATES FROM LOGISTIC REGRESSION MODEL

Variable	Crude OR (95% CI)	Adjusted OR (95% CI)[1]
Greater BMI at age 40	1.89 (1.11–3.23)	2.01 (1.16–3.50)
Less educated	2.33 (1.21–4.49)	2.02 (1.01–4.08)
Unmarried	2.91 (0.97–8.67)	2.26 (0.75–6.84)
No prior screening	2.20 (1.08–4.49)	2.36 (1.09–5.10)

[1]Simultaneously adjusted for other variables in model.

Since there were no significant differences in any of the variables studied between these 2 comparison groups, we report only the combined comparison data. Cases with lower Gleason scores were younger at diagnosis, were the most likely (92.8%) to have had prostate screening, were less likely to be current smokers (3.6%), and reported the fewest pack-years of smoking before diagnosis (21.5 *vs.* 28.6 years for high-score cases and 30.1 for the comparison group). They were also more likely to report never using alcohol (19.3%; data not shown). Although low Gleason score cases were not distinguishable by current weight, weight at age 40, or weight at age 25, they had the lowest average weight gain from ages 25 to 40 (4.6 *vs.* 6.3 kg for high-score cases).

Table IV summarizes the results of the best-fitting logistic regression model that included all relevant covariates. Higher BMI at age 40 (OR = 2.01, 95% CI 1.16–3.50), less education (OR = 2.02, 95% CI 1.01–4.08), not being married (OR = 2.26, $p > 0.05$), and not having had prostate cancer screening (OR = 2.36, 95% CI 1.09–5.10) were significant predictors of higher volume and/or extracapsular extension.

DISCUSSION

A critical goal in prostate cancer research is identifying determinants of the progression from focal non-significant prostate cancer to clinically overt disease. While Gleason scores above and below 7 are good predictors of future outcome, contemporary predictive methods are unable to identify which men with a Gleason score of 7 have clinically insignificant tumors that will not progress and which men will develop highly aggressive prostate cancer. Tefilli and associates (1999) evaluated pathologic characteristics and disease-free survival in 652 prostate cancer patients with Gleason scores of ≤6, 7, and ≥8. Patients with Gleason 7 were significantly different from the other groups with respect to incidence of organ-confined disease, positive margins, and disease-free survival. Graefen *et al.* (1999) studied 318 consecutive

patients who underwent radical prostatectomy and noted that the number of pre-operative biopsies with predominant Gleason grade 4 and/or 5 and the volume of cancer were the most accurate predictors of biochemical failure. In our series of patients, 12 men progressed biochemically. All were in the high-volume group.

Our findings suggest that early adulthood weight gain and smoking are important predictors of prostate cancer with higher Gleason scores. Men in the most favorable subgroup (those with low-volume disease and low Gleason scores) reported the lowest weight gain and least tobacco use. Obesity and smoking modulate the endocrine milieu and therefore could play an etiologic role in prostate cancer. BMI is strongly correlated with tissue density and therefore with lean body mass as well as fat mass (Garn *et al.,* 1986). A positive association of BMI with prostate cancer risk has been reported in several prospective and case-control studies (Chyou *et al.,* 1994; Garfinkel, 1985, Lew and Garfinkel, 1979; Talamini *et al.,* 1986; Thompson *et al.,* 1989; Snowdon *et al.,* 1984). However, other studies found no association (Wynder *et al.,* 1971; Ross *et al.,* 1987; Kolonel *et al.,* 1988; Mettlin *et al.,* 1989; Severson *et al.,* 1988; Hirayama, 1975; Schuman *et al.,* 1982; Whittemore *et al.,* 1985; Greenwald *et al.,* 1974). These inconsistent results could be due to subtle effects, attenuation of effects by measurement error, or biologically heterogeneous case groups. Most studies have not distinguished prostate cancer on the basis of Gleason score, tumor volume, or organ confinement and have focused instead on prostate cancer incidence or on fatal prostate cancer as the outcome.

Lew and Garfinkel (1979) reported that obesity was positively associated with "fatal" prostate cancer. Andersson *et al.* (1997) evaluated data from a 20-year follow-up of Swedish construction workers. Higher anthropometric measurements were positively associated with risk of prostate cancer and more strongly related to mortality than to incidence. The excess risk of death from prostate cancer was statistically significant in all BMI categories above the reference category: relative risk 1.40 (95% CI 1.09–1.81) in the highest category compared with the lowest (p for trend = 0.04). Cerhan *et al.* (1997) reported that greater BMI (relative risk = 1.7 for higher BMI, p for trend = 0.1) was an independent predictor of prostate cancer risk, and this association with risk was stronger for regional or disseminated disease at diagnosis. In a case-control study of 329 prostate cancer patients, obese men had a tendency to progress from stage B1 through D1, though no effect of smoking was detected (Furuya *et al.,* 1998). However, in a cohort study of Seventh Day Adventists, Mills *et al.* (1989) were unable to find an association between BMI and prostate cancer incidence.

Gronberg *et al.* (1996) noted a trend for increased BMI in subjects with prostate cancer ($p = 0.015$), with an OR of 1.44 for 26 to 29 kg/m^2 and 1.80 (95% CI 1.07–3.04) for BMI >29 kg/m^2 compared with BMI <23 kg/m^2. In a Japanese–Hawaiian cohort of almost 8,000 men and 306 incident cases of prostate cancer, Chyou *et al.* (1994) reported that the association between body weight and prostate cancer incidence was greater as the time interval from examination to diagnosis increased.

Weight, monitored over time, can serve as a surrogate measure of past and present dietary status. The affluent Western diet, characterized by animal fats, highly processed foods, and refined carbohydrates, is an energy-dense diet that results in an energy disequilibrium and increased risk of obesity. In their study of white, black, and Asian American men, Whittemore *et al.* (1985) confirmed that saturated fat intake is a significant predictor of risk, especially for advanced cases. However, they reported no significant differences in body mass. Gann *et al.* (1994) reported that men with elevated levels of plasma α-linolenic acid have a 2- to 3-fold increase in risk of prostate cancer. There were only 12 men with focal prostate cancer in their group, and the investigators proposed that lipids had a late-stage effect on prostate cancer growth.

Obesity can exert physiological effects on the hormonal milieu. Unsaturated fatty acids may regulate androgen activity in target cells by altering the activity of 5-α-reductase, which converts testosterone to 5-α-dihydrotestosterone (Liang and Liao, 1992). Obesity itself is associated with higher estrogen and lower testosterone levels (Zumoff, 1988), a profile that appears to predict a lower risk of prostate cancer but not of survivorship. Kato *et al.* (1992) showed that sex hormone–binding globulin levels and the ratio of testosterone to estrone and estradiol decrease progressively with increasing BMI. Wu *et al.* (1995) also evaluated bioavailable testosterone in 4 ethnic groups of men and showed that the age-adjusted concentrations of all androgen measures and sex hormone–binding globulin decrease with increasing BMI.

Essential fatty acids influence cell proliferation, tissue invasiveness, and metastatic potential (Karmali, 1987). Ross and Henderson (1994) suggested that dietary fat may interact with androgens early in life. For example, high fat intake in childhood might advance the onset of puberty (and thus increase lifetime exposure of the prostate to circulating testosterone) and in adulthood might directly increase circulating testosterone levels. Most studies of weight and prostate cancer risk have focused on adult BMI, though the early adulthood hormonal milieu might profoundly affect the prostate gland once it has fully developed (Giovannucci *et al.,* 1997). Similarly, Magnusson *et al.* (1998) have shown that weight gain after age 18 is a strong predictor of breast cancer risk. Uhley *et al.* (1997) demonstrated that chronic weight changes increase oxidative DNA damage in the mammary glands of female rats.

Our findings differ from those of Giovannucci *et al.* (1997), who reported that obesity at ages 5 to 10 has a negative association with aggressive prostate cancer. Their study included extracapsular and organ-confined cancers and those of undetermined stage (about 20% of the sample). We did not have comparable data on weight change at this age. Although we found no differences in height between the 2 groups of men with prostate cancer, height has been positively associated with prostate cancer risk in the Physician's Health Study (Hebert *et al.,* 1997).

Mukherjee *et al.* (1999) have demonstrated that restriction of energy intake (whether from fat, lipid, or carbohydrate) inhibits tumor growth and expression of vascular endothelial and insulin growth factors. Tumor growth was independent of the proportion of fat in the diet (Mukherjee *et al.,* 1999). As Bosland *et al.* (1999) pointed out in their accompanying editorial, the epidemiologic data concerning dietary fat and total energy intake are conflicting. This difficulty is compounded if one wants to differentiate between early and more advanced disease.

Another explanation for the link between diet and prostate cancer is related to carcinogens formed during the cooking of meat (Sugimura *et al.,* 1981). Many such exogenous compounds readily concentrate in prostatic fluid. Isaacs and Carter (1991) hypothesized that the chronic contact of prostatic glandular cells with luminal fluid is important in the etiology of prostate cancer.

Inconsistent associations between smoking and prostate cancer risk have been reported. Hsing *et al.* (1990) found a relative risk of 1.8 for smoking. A case-control study also showed evidence that smoking increases risk of prostate cancer, with a reported OR of 1.9 (Honda *et al.,* 1988). Other case-control studies have found no evidence for such an association (Severson *et al.,* 1989; Fincham *et al.,* 1990). Only 1 study has reported that smoking is associated with a higher tumor-specific mortality rate and a more aggressive phenotype (Daniell, 1995). Cerhan *et al.* (1997) reported that cigarette smoking (relative risk = 2.9 for currently smoking $\geq$20 cigarettes/day compared with never smoking; p trend = 0.009) was a risk factor for prostate cancer, and these associations were stronger for regional or disseminated disease at diagnosis.

There are inherent limitations in our study. Cases were not identified through a population-based registry and include prevalent cases. The patient population of the M.-D. Anderson Cancer Center is subject to the vagaries of referral patterns. Furthermore, we do not have a classic non-diseased control group for comparative purposes. However, the underlying hypotheses are

based on identifying epidemiologic differences between 2 groups of men with prostate cancer and not on identifying risk factors for prostate cancer *per se*. Moreover, both groups of men had prostate cancer; thus, recall bias should not be a concern. Also, our cases are similar to other reported hospital series with respect to grade, PSA levels, and age (Stamey *et al.*, 1999). Because of the small number of cases, we selected a high and variable control-to-case matching ratio. Hennessy *et al.* (1999) suggested that meaningful increases in statistical power can be obtained by increasing the control-to-case ratio when the number of available cases is small.

In summary, early adulthood weight gain and smoking may be associated with more aggressive prostate cancer, and low-volume, low-score disease is more likely to be diagnosed in routinely screened men. Our data also demonstrate that screening is associated with diagnosis of lower-volume and lower-score disease.

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