



Lifestyle and Anthropometric Risk Factors for Prostate Cancer in a Cohort of Iowa Men

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PURPOSE: Several lines of evidence suggest that prostate cancer has a hormonal etiology. We evaluated factors known to modulate the endocrine system, including alcohol and tobacco use, physical activity, and obesity as risk factors for prostate cancer.

METHODS: Cancer-free controls ($n = 1572$) who participated in a population-based case-control study from 1986–1989 (81% response rate) were followed through 1995 for cancer incidence by linkage to the Iowa Cancer Registry; 101 incident prostate cancers were identified.

RESULTS: Compared with non-users of alcohol, men who consumed <22 grams alcohol per week (relative risk [RR] = 1.1; 95% Confidence Interval [CI] 0.6–2.1), 22–96 grams alcohol per week (RR = 2.6; 95% CI 1.4–4.6) and >96 grams alcohol per week (RR = 3.1; 95% CI 1.5–6.3) were at increased risk of prostate cancer after adjustment for age, family history of prostate cancer, body mass index, total energy, and intake of carbohydrate, linoleic acid, lycopene, retinol, and red meat (p for trend < 0.0001). The respective RRs were similar when assessing type of alcohol consumed (beer, wine or liquor) or when well-differentiated, localized tumors were excluded. Body mass index was only weakly and positively associated with prostate cancer after adjustment for age (p for trend = 0.3), but this association strengthened after multivariate adjustment (p for trend = 0.08) and exclusion of well-differentiated, localized tumors (p for trend = 0.03). For the latter tumors, men with a BMI of 24.1–26.6 kg/m^2 (RR = 1.5; 95% CI 0.7 – 3.0) and >26.6 kg/m^2 (RR = 2.1; 95% CI 1.1–4.3) were at elevated risk compared to men with a BMI <24.1 kg/m^2 . Tobacco use (cigarettes, cigar/pipe, chewing tobacco and snuff use), height, weight, and both leisure and occupational physical activity were not associated with risk of prostate cancer in this cohort.

CONCLUSIONS: These data suggest that in white men obesity is a risk factor for more clinically significant prostate cancer and confirm limited previous reports showing that alcohol consumption is positively associated with prostate cancer and that this risk is not limited to any specific type of alcohol. *Ann Epidemiol* 2000;10:361–369. Published by Elsevier Science Inc.

KEY WORDS: Obesity, Physical Activity, Prostate Cancer, Smoking.

INTRODUCTION

The American Cancer Society has estimated that over 184,000 men will be diagnosed with prostate cancer in the United States during 1998 (1). In addition, prostate cancer has risen to be the second leading cause of cancer-related death in the United States (2). Identifying risk factors for prostate cancer has been the subject of many epidemiological studies focusing on environmental and genetic factors,

but there are currently few well established risk factors beyond age, race and family history (3).

There continues to be a strong interest in evaluating the role of steroid hormones in the etiology of prostate cancer, because many of these hormones, particularly testosterone, are integral to the normal growth and maintenance of the prostate gland (4, 5). We therefore evaluated the role of lifestyle (alcohol, smoking, and physical activity) and anthropometric (weight, height, and body mass) factors known to correlate with or modulate endogenous steroid hormones as prostate cancer risk factors in a population-based cohort of Iowa men.

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MATERIALS AND METHODS

Study Population

We used a population-based control group to form a retrospective cohort; full details are available elsewhere (6).

Selected Abbreviations and Acronyms

BMI = body mass index

CI = confidence interval

RR = relative risk

Briefly, a population-based, case-control study of six cancer sites was conducted in Iowa from 1986 through 1989 (7). Cases were individuals diagnosed with brain, kidney, bladder, colon, rectum, or pancreatic cancer, and were identified from the Iowa Cancer Registry. Controls were frequency matched by sex and five-year age group. Eligibility criteria for controls included Iowa residency, age 40–86 years old, living at the time of enrollment and no prior history of cancer. Controls were randomly selected from the Iowa population by two distinct sampling methods: 1) a random sample of all persons 40 to 64 years of age identified through the Iowa driver's license records and 2) a random sample of all persons 65 years of age and older identified through the US Health Care Financing Administration. Both sampling frames cover an estimated 95% or more of the Iowa population in those age groups (8, 9). Of the 1989 males invited to participate as controls, 1,601 agreed to participate (81% response rate). We further excluded controls who required a proxy respondent ($n = 24$), leaving a total of 1577 men forming the at-risk cohort.

Data Collection

Data were collected through a mailed questionnaire, supplemented with a telephone interview. Information collected included demographics, education, usual occupation (coded according to the U.S. Department of Commerce Standardized Industry and Occupation Codes for 1980), weight, height, family history of cancer, and usual adult diet using a 55-item food frequency questionnaire. Alcohol use was ascertained as part of the food frequency questionnaire that specifically asked about usual adult consumption of beer (12 ounce cans/bottles), wine (4 oz glass) and liquor (1 oz shot). Study subjects were specifically instructed to ignore recent changes in diet and alcohol use. Participants were also asked to report the frequency of strenuous or moderate exercise during most of their adult life.

Detailed data on tobacco use (cigarette, cigar and pipe smoking, snuff, and chewing tobacco) were collected, including ever use, age started and stopped, and for cigarette smokers, the number of cigarettes smoked per day. Pack-years of cigarette smoking were calculated based on duration of cigarette smoking and number of cigarettes smoked per day.

Follow-up

Prostate cancer incidence was ascertained by linking the cohort to the State Health Registry of Iowa's cancer data-

base, which is part of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program (2). Through 1995, 274 men were diagnosed with cancer, including 103 cases of prostate cancer. Two of the prostate cancers were diagnosed prior to the subjects return of the questionnaire and were excluded from further analysis, reducing the number of cases to 101 in an at-risk cohort of 1575 persons.

Vital status and residence in Iowa were ascertained by three different methods: linkage to Iowa's death certificate database, linkage to the HCFA Medicare enrollment database and linkage to the Iowa driver's license database. Three men did not link to any database (i.e., lost to follow-up) and were excluded, leaving 1572 in the at-risk cohort.

Statistical Analysis

Anthropometric variables (weight and height) were categorized into three levels based on the tertile cut-points in the at-risk cohort. Body mass index (BMI) was derived from the reported subject's weight (kg) divided by the subject's height (m) squared. To assess adult weight gain, percent change in BMI was defined as the most recent BMI divided by BMI at age 20, expressed as a percent. The percent BMI change was categorized *a priori* into five categories: >5% loss, within 5%, 5.1–10% gain, 10.1–15% gain and >15% gain.

Usual use of alcohol as an adult was coded as "no" or "yes", and individual types of alcohol were analyzed as servings per week with non-users of any alcohol as the reference group. We also summarized alcohol consumption in grams per week. For analysis, alcohol use (grams per week) was categorized based on the tertile distribution of use among alcohol consumers, and was compared to non-users.

Tobacco use was derived from use of any tobacco-related product (cigarettes, cigars/pipe, snuff or chewing tobacco). The referent group for all analyses was composed of men who never used any type of tobacco for more than six months. For all tobacco-specific analyses, tobacco use was then categorized as former or current user. A former user was defined as anyone who stopped using a tobacco product more than two years before baseline; a current user was defined as anyone using a tobacco product two years before baseline. This definition was used due to how the tobacco questions were asked in the original case-control design. Cigarette use was further categorized as former cigarette smoker, current smoker (less than a pack per day) and current smoker (more than a pack per day). Pack-years of smoking was categorized *a priori* based on commonly published cut-points (<25, 25–50, >50 pack-years).

Leisure physical activity was *a priori* reduced to three categories: very active (≥ 1 strenuous activities/day), moderately active (2–6 strenuous activities/week) and inactive (≤ 4 strenuous activities/month). Occupational physical ac-

TABLE 1. Age-adjusted^a relative risks of prostate cancer according to anthropometric measure and physical activity, Iowa, 1986-1995

	Cases	Person years	RR ^b	95% CI	<i>p</i> for trend
Height (m)					
<1.75	28	2555	1	referent	
1.75-1.79	25	2642	0.9	0.5-1.5	
>1.8	43	3826	1.1	0.7-1.7	0.2
Weight (kg)					
<74.8	22	2556	1	referent	
74.8-83.9	41	3403	1.4	0.8-2.3	
>83.9	33	2995	1.2	0.7-2.1	0.4
BMI (kg/m ²)					
<24.1	27	2831	1	referent	
24.1-26.6	31	3085	1.0	0.6-1.7	
>26.6	38	3032	1.3	0.8-2.2	0.3
Percent change in BMI from age 20 to most recent BMI					
>5.0% loss	1	525	0.2	0.02-1.5	
Within 5.0%	12	1357	1	referent	
5.1-10.0% gain	15	1345	1.3	0.6-2.7	
10.1-15.0% gain	14	1568	1.0	0.5-1.9	
>15.0% gain	51	4027	1.3	0.8-2.2	0.3
Leisure Physical Activity ^c					
Inactive	48	4628	1	referent	
Moderately active	26	2426	1.0	0.6-1.6	
Very active	17	1699	0.9	0.5-1.5	0.7
Occupational Physical Activity					
Inactive	18	1782	1	referent	
Moderately active	33	3224	1.0	0.6-1.8	
Very active	49	4498	1.0	0.6-1.8	0.9

^a Adjusted for age (40-64, 65-69, 70-74, 75-79, 80+) by the method of Mantel-Haenszel.

^b Relative risk (RR) and 95% confidence intervals (CI).

^c Inactive = ≤4/month; Moderately Active = 2-6/week; Very Active = ≥1/day.

tivity was categorized into three levels (very active, moderately active and inactive) according to the method of Garabrandt and colleagues (10) using the occupational codes.

Person-years of follow-up were calculated for each man from the date of receipt of the baseline questionnaire to the date of prostate cancer diagnosis, emigration from Iowa (5.3%), or death in Iowa (23.8%); if none of these occurred, follow-up was through December 31, 1995. Relative risks (RR) and 95% confidence intervals (CI) were used as the measure of association between these exposure categories and prostate cancer incidence. The Mantel-Haenszel procedure (11) was used to estimate age-adjusted RRs and Cox proportional hazards (12) regression was used to estimate multivariate-adjusted RRs.

RESULTS

The mean age of the cohort at baseline enrollment was 68.1 years (range, 40-86 years); 99% of the subjects were white, 87% were married and 25% had greater than a high school education. At baseline, 24% used tobacco and 57% used alcohol. The mean BMI was 25.8 kg/m² and 62% reported at least one strenuous leisure exercise session per month.

Through 1995 (9509 person-years of follow-up), 101 incident prostate cancers were identified. The mean age at diagnosis was 69.4 years (range, 55-84 years). Based on SEER Program staging data for prostate tumors, 63% were localized, 11% regional and 11% metastatic, and 15% were missing stage data.

Table 1 presents the age-adjusted relative risks of prostate cancer for several anthropometric variables, as well as physical activity. While there were slight elevations in risk among taller and heavier men as well as men who had increased in BMI since age 20, none of the risk estimates was statistically significant and there was no evidence of dose-response relations. There was no association between physical activity, recreational or occupational, and prostate cancer risk.

The age-adjusted relative risks in Table 2 show that men who reported consuming any alcoholic beverages were at increased risk of prostate cancer (RR = 1.7; 95% CI 1.1-2.6), and there was a suggestion of a dose-response with increasing grams of alcohol consumed (*p* for trend = 0.03). The age-adjusted relative risks for types of alcohol (wine, liquor and beer) all showed positive associations with prostate cancer risk (*p* for trend = 0.02, 0.05 and 0.08, respectively).

TABLE 2. Age-adjusted^a relative risks of prostate cancer according to usual adult consumption of alcoholic beverages, Iowa, 1986-1995

	Cases	Person years	RR ^b	95% CI	p for trend
Any alcohol use					
No	30	3605	1	referent	
Yes	62	4937	1.7	1.1-2.6	0.02
Grams of alcohol user per week					
0	30	3605	1	referent	
<22	17	1599	1.4	0.8-2.5	
22-92	27	1710	2.1	1.2-3.5	
>92	18	1628	1.5	0.8-2.7	0.03
Wine (8 oz glass/week)					
None	30	3605	1	referent	
<0.2	6	628	1.2	0.5-3.0	
0.2-0.9	54	4584	1.5	0.9-2.4	
>0.9	11	775	1.9	0.9-3.7	0.02
Liquor (1 oz shot/week)					
None	30	3605	1	referent	
<0.5	12	1015	1.6	0.8-3.2	
0.5-2.5	41	3687	1.5	0.9-2.4	
>2.5	18	1285	1.7	0.9-3.0	0.05
Beer (12 oz cans/week)					
None	30	3605	1	referent	
<1	22	1182	2.4	1.4-4.3	
1-3	15	1441	1.3	0.7-2.5	
>3	19	1527	1.7	0.9-3.0	0.08

^a Adjusted for age (40-64, 65-69, 70-74, 75-79, 80+) by the method of Mantel-Haenszel.

^b Relative risk (RR) and 95% confidence intervals (CI).

Tobacco use showed little association with prostate cancer risk (Table 3). No association was seen for pipe/cigar smoking (Table 3), or snuff and chewing tobacco (data not shown). There was a weakly suggestive positive association with cigarette smoking, and men who smoked ≥ 20 ciga-

rettes per day had a 60% increase in risk, although this estimate lacked precision (95% CI 0.7-3.9). However, there was no dose-response trend in pack-years smoked (p for trend = 0.5).

Because of the relatively strong positive association found

TABLE 3. Age-adjusted^a relative risks of prostate cancer according to smoking status, Iowa, 1986-1995

	Cases	Person years	RR ^b	95% CI	p for trend
Tobacco use ^c					
Never	24	2722	1	referent	
Former	55	4579	1.3	0.7-2.0	
Current	22	2290	1.2	0.6-2.0	0.6
Cigarette smoking status					
Never	24	2722	1	referent	
Former	56	4686	1.4	0.9-2.3	
Current (<20 cigs/day)	9	918	1.3	0.6-2.8	
Current (≥ 20 cigs/day)	7	691	1.6	0.7-3.9	0.2
Pack-years of smoking					
Never	24	2722	1	referent	
<25	29	2063	1.7	1.0-3.0	
25-50	21	2170	1.2	0.7-2.2	
>50	22	2046	1.4	0.8-2.5	0.5
Pipe/Cigar smoking status					
Never	24	2722	1	referent	
Former	13	1597	1.0	0.5-1.9	
Current	5	462	1.3	0.5-3.5	0.7

^a Adjusted for age (40-64, 65-69, 70-74, 75-79, 80+) by the method of Mantel-Haenszel.

^b Relative risk (RR) and 95% confidence intervals (CI).

^c Use of any of the following for more than six months: cigarettes, pipe, cigar, chewing tobacco, and snuff.

TABLE 4. Distributions of selected risk factors by level of usual adult alcohol consumption, Iowa, 1986-1989 (baseline data)

Risk factors	Alcohol use (grams/week)				p-value ^a
	(N = None)	≤22	23-92	>92	
	Means				
Age (years)	70.1	67.2	65.2	65.3	0.0001
Age at Diagnosis (years)	74.7	74.8	72.1	73.2	0.4
Height (meters)	1.77	1.78	1.77	1.77	0.02
BMI (kg/m ²)	25.9	25.9	26.0	25.6	0.5
Total Energy (Kcals/day)	1949	1916	1885	2183	0.0001
Dietary intake ^b					
Carbohydrates (g/d)	221.5	221.3	213.1	194.1	0.0001
Lycopene (μg/d)	541.6	514.2	511.8	516.5	0.6
Red meat (servings/week)	7.5	7.3	7.2	6.0	0.0014
Linoleic Acid (g/d)	10.4	10.6	10.6	9.4	0.0001
Retinol (IU/d)	1023.7	936.4	951.6	912.4	0.0001
	Percent distribution				
Family history of prostate cancer in a father or brother	4.8%	5.7%	5.3%	3.5%	0.7
Education					
<High School	28.7%	21.3%	17.4%	17.0%	
High School	52.9%	45.5%	47.8%	50.4%	
>High School	18.4%	33.2%	34.8%	32.6%	0.001
Tobacco use					
Never	36.2%	28.9%	22.4%	10.5%	
Former	45.1%	49.6%	56.3%	50.4%	
Current	18.7%	21.5%	21.3%	39.1%	0.001
Leisure physical activity ^c					
Inactive	55.0%	53.7%	52.2%	50.0%	
Moderately active	23.7%	28.3%	30.4%	32.8%	
Very active	21.3%	18.0%	17.4%	17.2%	0.2
Occupational physical activity					
Inactive	12.8%	22.0%	25.6%	26.6%	
Moderately active	31.7%	33.5%	30.0%	39.9%	
Very active	55.5%	44.5%	44.4%	33.5%	0.001

^a p-value is either for global test for differences among means or chi-square test for differences in proportions, as appropriate.

^b Adjusted for total energy.

^c Inactive = ≤4/month; Moderately active = 2-6/week; Very active = ≥1/day.

with alcohol consumption in this cohort, we evaluated differences in several potential risk factors across alcohol levels. Table 4 shows that there was an inverse relationship between alcohol consumption and study subject's age at baseline, while there were no differences in the age at diagnosis of prostate cancer. There were no striking differences for height and BMI across levels of alcohol consumption, although the differences in height were statistically significant. Total caloric intake was greater in heavy drinkers (2183 kcal/day) compared to non-drinkers (1949 kcal/day). There was also an inverse relation between alcohol use and intake of protein, carbohydrates, red meat and linoleic acid, while there appeared to be no differences with lycopene. There was little or no difference in the percent distribution among differing levels of alcohol use related to family history of prostate cancer. Education levels appeared to be linked to alcohol consumption, with more educated men using more alcohol. There was a positive association between

smoking and alcohol use; 39.1% of the highest drinkers (>92 g/week) were current smokers compared to 18.7% of the non-alcohol users. While there was no difference in leisure physical activity across levels of alcohol consumption, occupational physical activity showed an inverse association.

The final multivariate model is presented in Table 5. After adjustment for several prostate cancer risk factors in this cohort (age, family history of prostate cancer, total energy, and intake of carbohydrate, linoleic acid, lycopene, retinol, and red meat) the association for both alcohol consumption (*p* for trend < 0.001) and BMI strengthened (*p* for trend = 0.08). Further adjustment for smoking or physical activity did not alter these findings (data not shown).

To evaluate the association of alcohol consumption and more clinically significant prostate cancer, we excluded localized, well-differentiated prostate cancers and re-fit the multivariate model (see Table 5). The positive association

TABLE 5. Multivariate-adjusted relative risks of prostate cancer according to alcohol consumption and body mass index, Iowa, 1986-1995

	All prostate cancer (n = 81)			Significant disease ^a (n = 57)			Stage at diagnosis ^b					
							Local disease (n = 53)			Regional/Distant disease (n = 18)		
	Cases	RR ^c	95% CI	Cases	RR ^c	95% CI	Cases	RR ^c	95% CI	Cases	RR ^c	95% CI
Alcohol (g/week)												
None	26	1	referent	19	1	referent	17	1	referent	4	1	referent
<22	14	1.1	0.6-2.1	9	1.0	0.4-2.1	11	1.4	0.6-3.0	2	0.9	0.3-5.0
22-92	25	2.6	1.4-4.6	20	2.7	1.4-5.3	15	2.5	1.2-5.2	7	4.5	1.2-16.9
>92	16	3.1	1.5-6.3	9	2.1	0.7-5.4	10	3.3	1.3-8.1	5	6.4	1.4-29.7
<i>p</i> for trend		0.001			0.009			0.003			0.006	
BMI (kg/m ²)												
<24.1	23	1	referent	13	1	referent	14	1	referent	5	1	referent
24.1-26.6	25	1.1	0.6-1.9	19	1.5	0.7-3.0	18	1.3	0.6-2.7	2	0.3	0.1-1.2
>26.6	33	1.6	0.9-2.8	25	2.1	1.1-4.3	21	1.8	0.9-3.7	11	2.5	0.9-7.5
<i>p</i> for trend		0.08			0.03			0.09			0.02	

^a Significant disease was defined as the exclusion of all well-differentiated, localized prostate cancers.

^b Based on SEER staging codes.

^c Relative risk were adjusted for age, body mass index, total energy, carbohydrates, linoleic acid, lycopene, retinol, red meat and family history of prostate cancer.

with alcohol use remained (*p* for trend = 0.009), although the risk estimate for the heaviest drinkers attenuated. In addition, the association with BMI strengthened (*p* for trend = 0.03) and the upper point estimate excluded the null value. The associations for height, smoking and physical activity with significant prostate cancer were not materially different than those already presented in Tables 1 and 3 for all prostate cancer (data not shown).

We also stratified the results by stage at diagnosis (local versus regional/distant). Although based on small numbers, this analysis suggests that the alcohol association is stronger for regional/distant disease (see Table 5).

DISCUSSION

Alcohol

In this population-based cohort study of Iowa males, alcohol consumption, irrespective of alcohol type, was associated with an elevated age-adjusted relative risk of prostate cancer, and this association was stronger and demonstrated a clearer dose-response relation after further adjustment for family history of prostate cancer, BMI, total energy and intake of carbohydrate, linoleic acid, lycopene, retinal, and red meat.

Several studies conducted among alcoholics (13, 14) or the general population (15-19) have reported either suggestive or statistically significant positive associations. The most comprehensive study reported to date was a large, population-based case-control study conducted in the United States by Hayes et al. (18). They reported a positive association between alcohol consumption and prostate cancer (*p* < 0.001), with men at the highest consumption category (>57 drinks per week), showing a 90% increase

in risk (95% CI 1.3-2.7) compared to never users. In addition, risks were elevated across all types of alcohol, equivalent for both blacks and whites, and not confounded by a variety of prostate cancer risk factors including education, income, BMI, caloric intake, fat intake, fruit and vegetable consumption, history of liver cirrhosis, and family history of prostate cancer. Positive studies with lower levels of overall consumption have shown similar levels of risk (16, 17, 19). Both our data and that of Hayes et al. (18) also suggest that alcohol is a stronger risk factor for higher grade disease.

While our data are consistent with the studies discussed above, most studies published to date (reviewed in 20) show no association between alcohol use and prostate cancer, while a few show an inverse association. Both positive and null/inverse results have been reported from studies conducted in a variety of populations using both population-based case-control and cohort study designs, and the current epidemiologic literature cannot be easily reconciled, and could be interpreted as random variation across studies, arguing against a true association.

There are several potential mechanisms by which alcohol consumption could influence prostate carcinogenesis. One of the earliest suggested mechanisms linked the hormonal effects of alcohol use to prostate cancer risk, in part reflecting a long-standing interest in the role of hormones in prostate cancer (4). Acute consumption of alcohol depresses testosterone levels, and long-term, chronic alcohol ingestion seen in alcoholics with liver damage is associated with a state of hyperestrogenism (21); these observations would predict lower risk of prostate cancer with alcohol use. However, no deficit and possibly an excess of prostate cancer has been noted in studies of alcoholics (13, 14, 22). In addition, moderate consumption of alcohol shows little correlation

with serum androgen concentrations (23, 24), and thus this mechanism is not likely to be relevant to the general population. Other hormonal mechanisms have been less explored, but one intriguing mechanism is through insulin-like growth factor-I (IGF-I), which is mitogenic for prostate epithelial cells (25). In the Rancho Bernardo Study, there was a strong positive association between IGF-I levels and alcohol use (26), even at very moderate levels of consumption (1–2/drinks per month). Plasma IGF-I showed a strong positive association with prostate cancer in a recent nested case-control study from the Physician's Health Study (27). These observations clearly warrant further investigation.

More direct mechanisms have also been postulated. A variety of compounds found in alcoholic beverages are known or suspected carcinogens in animals, although evidence for carcinogenic effects of these compounds in humans is often weak or not available (28). In addition, many of these compounds are specific to a particular type of alcohol, and thus cannot explain a general alcohol effect. In contrast, acetaldehyde, the major metabolite of alcohol, has been shown to cause cancer in animals models (29), but there is inadequate evidence for its carcinogenicity in humans (28). Little is known about the effects of acetaldehyde or other alcohol metabolites on the prostate gland *per se*, but the prostate does contain aldehyde dehydrogenase, which is important in detoxification of a variety of oxidation products produced there (30). Alcohol or its metabolites may alter other enzymatic pathways with relevance to carcinogenesis. For example, long-term ingestion of ethanol increases the level of cytochrome P450 in the liver, which alters the metabolism of a variety of carcinogens and co-carcinogens (28).

Finally, alcohol could be related to prostate cancer indirectly through dietary effects including nutrient displacement, deficiency in nutrients that are putative protective agents, and malabsorption (31). However, these mechanisms seem less plausible in explaining an association with moderate alcohol consumption in this population, which appears to be well nourished. Also, there is little evidence for strong confounding by dietary variables in our data or that of Hayes et al. (18).

Smoking

We found little evidence for an association between cigarette smoking and prostate cancer, although men who smoked ≥ 20 cigarettes per day at baseline were at a 60% elevated risk compared to never tobacco users. However, this point estimate lacked precision, possibly reflecting a lack of study power. In addition, there was no evidence suggesting a dose-response relation with cigarette use or pack-years of smoking.

Nomura and Kolonel (3) and Rodriguez et al. (32) both provide summaries of epidemiological studies that have fo-

cused on cigarette smoking and prostate cancer and they find no consistent evidence that cigarette smoking is positively associated with prostate cancer incidence. However, there is some evidence that cigarette smoking may be associated with more aggressive (33) or fatal (32,34–36) prostate cancer.

There are several hypothesized biological mechanisms related to cigarette smoking and prostate cancer. N-nitroso compounds have been shown to induce prostate cancer in laboratory rats (37) and these compounds have been found to be excreted in the urine of smokers (38, 39). Smokers also have elevated levels of serum androstenedione and testosterone (presumptive contributors to the progression of prostate cancer) and estrogen (thought to limit progression of prostate cancer) (40, 41), although the findings have not been universal (24). Epidemiologic and biologic data to date suggest that smoking is not likely to be a major risk factor for prostate cancer incidence but rather may be more important in progression and survival (42).

Anthropometric Factors

In the age-adjusted model, we found a weak positive association between body mass and prostate cancer, which strengthened after multivariate adjustment and exclusion of well differentiated, localized prostate cancers. Case-control studies of body mass and prostate cancer have nearly all been null (4), while cohort studies have shown both positive (43–46) and null (47–49) associations. This and one other study (33), but not a third (49), found that body mass was positively associated with more aggressive prostate cancer. The latter finding is of interest, since most cohort studies of prostate cancer mortality have reported positive associations (50, 51), suggesting that body mass may also play a role in prostate cancer aggressiveness. The biologic mechanisms underlying such an association are not known, but hormonal alterations associated with obesity, including increased levels of estrogen and sex hormone binding globulin and decreased levels of total, bioavailable, and free testosterone (23, 24) are thought to be important, although these observations would predict an inverse association. However, body mass index is less able to distinguish fat and lean tissue, and lean tissue (muscle mass) may be associated with both higher androgen levels and increased prostate cancer risk (43). Unfortunately, we cannot evaluate this possibility in this dataset.

Physical Activity

In this cohort, both leisure and occupational physical activity were not associated with prostate cancer. Oliveria (52), in a review of epidemiologic studies on physical activity and prostate cancer, reported three studies (two cohort and one case-control) showing a positive association; nine studies (six cohort and three case-control) showing an inverse

association; and five studies (one cohort and four case-control) showing null results. Several occupational studies have been conducted in which job-related physical exertion was assessed with respect to prostate cancer (53-55), with most reporting that lower occupational activity (referent to highly active) had a slight increase in the risk of developing prostate cancer.

Limitations and Strengths

All exposures were self-reported, and for alcohol and physical activity, were based on usual adult levels; thus variation over the life span, including adolescent exposure, were not available. Occupational physical activity was derived based on job title provided by each study subject, and this method has many limitations (10). In addition, the physical activity measures were not able to accurately account for duration and intensity of activity.

In our cohort, the alcohol consumption distribution was on the lower end of total alcohol consumption of previous reports comparing alcohol and prostate cancer, and the lack of higher exposures limits our ability to fully define the dose-response curve.

A final limitation of this study is that the cohort was 99% white, and this limits generalizability. However, the case-control study by Hayes et al. (18) found no differences in the age-adjusted point estimates for the association between alcohol use and prostate cancer between blacks and whites.

The strengths of this study included the use of a population-based sample with a high participation and a prospective cohort study design, which allow the direct comparison of incidence rates between exposed and unexposed study subjects. Another strength of this study was the use of a SEER cancer registry for case ascertainment of prostate cancers. This study also adjusted for major potential confounding factors related to prostate cancer, including diet and family history of either prostate or breast cancer.

SUMMARY

We found that the consumption of alcohol increased the risk of prostate cancer in an age-adjusted model and the point estimates were strengthened after adjusting for several other known or suspected risk factors. Additionally, there was a positive association between body mass and significant prostate cancer. There were no associations evident for height and weight, physical activity and tobacco use.

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