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Smoking, Alcohol Drinking, and Risk for Prostate Cancer

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Abstract

Smoking, Alcohol Drinking, and Risk for Prostate Cancer

By Yueqing Wang

Background:

Prostate cancer is the most common cancer among men in the United States. Smoking and alcohol drinking are considered as both the initiator and promoter of cancer carcinogenesis, however, their role in prostate cancer is unclear. In this study, we investigated whether smoking and alcohol drinking are associated with risk of incident prostate cancer overall and by tumor severity.

Methods:

The data were analyzed from a case-control study of incident prostate cancer (n=112) and community-based controls (n=255) conducted in North Carolina between 1994 and 1996. A four- to five-hour study visit with multiple questionnaires was used to collect demographic, dietary, and lifestyle information from all participants. The cancer severity was categorized based on TNM stage. The assessment of smoking and alcohol drinking was based on both lifestyle and block food frequency questionnaire. Logistic regression analyses were conducted to calculate crude and multivariable adjusted odds ratio (ORs) and corresponding 95% confidence intervals (95% CIs).

Results:

There were no significant associations between smoking, alcohol drinking and overall incident prostate cancer. Compared with never smokers, current smokers had a statistically non-significant higher risk of prostate cancer (multivariable OR=1.54, 95% CI: 0.62-3.82), but not former smokers (multivariable OR=0.98, 95% CI: 0.56-1.73). Among former smokers, those who smoked for ≥ 25 years had a significantly lower risk of localized disease (multivariable OR_{localized}=0.41, 95% CI: 0.17-0.96); however, the sample size was relatively small for this analysis. Compared with non-alcohol drinkers, former alcohol drinkers had a statistically non-significant higher risk for localized and advanced prostate cancer (multivariable OR_{localized}=1.61, 95% CI: 0.75-3.47; multivariable OR_{advanced}=1.55, 95%CI: 0.54-4.47, respectively); while current alcohol drinkers had a statistically non-significant higher risk for advanced prostate cancer (multivariable OR_{advanced}=1.40, 95%CI: 0.53-3.71).

Conclusion:

Overall, tobacco smoking and alcohol consumption were not associated with risk for incident prostate cancer.

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CHAPTER 1: BACKGROUND

Descriptive Epidemiology

Incidence and Mortality

Prostate cancer is the most frequently diagnosed malignant cancer and the second most common cause of cancer death in American men. According to the American Cancer Society's estimates in 2014, about 233,000 new cases of prostate cancer will be diagnosed and 29,480 men will die of it in the United States. About 1 man in 7 will be diagnosed with prostate cancer during his lifetime and 1 man in 36 will die of it [1]. Prostate cancer survival rates vary by stage at diagnosis: patients with metastatic castration-resistant prostate cancer has a median survival of 9 to 30 months while the median survival for non-castrate metastatic prostate cancer is 6.6 years.

Globally, prostate cancer is the third most common cancer, with more than 903,500 cases diagnosed and 258,400 death in 2008 [2]. The disease burden shows remarkable worldwide variation. The incidence rates appear highest in westernized countries and lowest in Asian countries. In the late 1980s, a 30-fold difference in incidence was noted between population groups, with the highest in African-American men in the United States and the lowest in Japanese and Chinese men living in their native countries [3]. In early 2000s, the prostate cancer incidence variation has reached up to more than 70-fold between populations around the world [4]. The wide variation is likely due to differences in detection, treatment, lifestyle and genetic factors.

Migrant Studies

Migrant studies have demonstrated that when men migrate from low to high risk countries, the incidence rates increase but do not reach up to the full risk profile of those born as natives in high risk countries. In studies of Japanese in Los Angeles County, prostate cancer risk of

Japanese immigrants is much higher than that of their homeland counterparts yet still below that of US born Japanese men [5]. Although a shift toward higher incidence rates with migration to high risk countries may be due to different or more advanced screening tests, the similar trend in mortality suggests an environmental cause.

Prostate Cancer Pathogenesis

Prostate cancer has one of the strongest heritable components of any cancers. Results from two twin studies suggested that about 30% to 40% of prostate cancer risk can be explained by genetic factors [6, 7]. Epidemiological studies provided additional evidence supporting the role of familial factors. According to self-reported prostate cancer occurrence among study participants' father or brothers, findings from two case-control studies [8, 9] and two cohort studies [10, 11] showed that men with first-degree relatives with prostate cancer had a two- to four-fold increase in risk of the disease. Risk was greater for participants who have more than one brother with prostate cancer, suggesting that maternal factors (e.g., mitochondria) might play a role. Also, the association appeared to be stronger for prostate cancer patients with early disease onset. Subsequently, an X-linked or recessive model of inheritance was proposed to explain the excessive risk with an affected brother compared to those with an affected father [12]. In 1998, a prostate cancer susceptibility locus was identified on chromosome X (Xq27-28), a finding supporting an X-linked mode of hereditary prostate cancer (HPC) inheritance [13]. Several other possible prostate cancer susceptibility loci were identified in a multi-stage genome-wide association study (GWAS), including regions on chromosomes 2p, 3q, 5p, 6p, 12q [14]. More than 40 prostate cancer susceptibility loci have now been identified, with which approximately 25% of familial risk can be explained, while few high penetrance genes have been fully characterized.

The most compelling evidence for the role of genetics in prostate cancer exists for a common variant on chromosome 8 (8q24), a region initially identified through a study of Icelandic families. The genome-wide linkage scan suggests a possible linkage signal on chromosome 8q24 with a maximum LOD score of 2.11. Additional markers on chromosome 8 have been genotyped, and identified that a variant allele at microsatellite DG8S737 is associated with a higher risk of prostate cancer: a 62% increased risk of the disease in three case-control series of European ancestry from Iceland (OR=1.62, P-value: 2.7×10^{-11}), Sweden and the U.S. The association was then replicated and validated in an African American population (OR=1.60, P-value = 0.0022), explaining a greater estimated population attributable risk (PAR) contributing to higher incidence of the disease among African American (PAR=16%) than men of European ancestry (PAR=5%-11%) [15].

Numerous studies have examined the association between low penetrance susceptibility polymorphisms in candidate genes and prostate cancer risk. While significant SNPs have been reported [16, 17], many of these associations could not be replicated in subsequent studies or inconsistent associations may be found. The difficulty in replicating earlier findings in subsequent studies is due, in part, to 1) the relatively small to modest effects of most common polymorphisms; 2) the relatively small sample sizes to detect modest effects; 3) the tendency of small studies to produce false positive finding, and 4) differences in study design and populations, including differences in severity of cases [18]. As suggested, at least >1,000 cases are necessary to clarify further the role of known polymorphic markers.

Androgen Receptor

The normal development and progression of the prostate is dependent on androgen acting through the androgen receptor (AR). AR belongs to the steroid hormone group of nuclear receptors and has a strong influence on prostate cell division *via* testosterone and

dihydrotestosterone. Genetic variation in AR exists, including a polymorphic CAG repeat sequence that is inversely associated with transcriptional activity. The normal range of the number of CAG repeats is thought to be between 9 and 30 [19]. Short CAG repeat length are specifically associated with development of TMPRSS2: ERG-positive prostate cancer [20]. The average number of CAG repeats has been found to vary among different races, which indicates the race-specific prostate cancer risk [21].

As the dependence of prostate cancer cells on androgen stimulation first described by Huggins and Hodges [22], androgen binds to the AR and then translocates to the nucleus. The binding of this complex with androgen responsive elements affects the transcription of androgen-regulated gene, which further stimulates proliferation and inhibits apoptosis of prostate cancer cells. Apart from androgen-dependent prostate cancer, there are several molecular mechanisms for the development of castration-resistant prostate cancer (CRPC), or androgen-independent prostate cancer (AIPC). Prostate cancer cells turn to be hypersensitive to androgen stimulation with even low level of AR expression. Autocrine and paracrine production of androgens is unregulated in CRPC, which may activate AR via steroids. Moreover, in CRPC, several bypass pathways were identified that contribute to cancer cell growth, such as interleukin-6 (IL-6) signaling [23, 24]. Served as glycoprotein, IL-6 is implicated in progression to CRPC [25]. IL-6 has been found frequently expressed in prostate cancer cell lines, as early as benign hyperplasia, and the expression increases in patients with metastatic disease. IL-6 activates AR-mediated gene expression by activation of the AR through a STAT3 pathway in androgen-dependent LNCap cells [26, 27]. Overexpression of IL-6 increases PSA mRNA in LNCap cells, which stimulate the growth of these cells. Other signaling pathways, such as Src-mediated and insulin-like growth factor (IGF) may also allow non-genomic signaling through AR after deletion of androgen [24].

Demographic Factors

Age: Although only 1 in 10,000 men under age 40 will be diagnosed with prostate cancer, the rate increases up to 1 in 38 for age 40 to 59, and 1 in 14 for age 60 to 69 [28]. About 6 in 10 cases of prostate cancer are found in men over the age of 65. The average at the time of diagnosis in the United States is about 69.

Race/ethnicity: Prostate cancer occurs more often in African-American men and Caribbean men of African ancestry than in men of other races. African-American men are also more likely to be diagnosed at an advanced stage, and 2.5 fold higher prostate cancer mortality relative to white men [29]. The rate of men getting the disease or dying from it varies by race and ethnicity, black men has the highest rate of getting and dying of prostate cancer, followed by white, Hispanic, American Indian/Alaska Native, and Asian/Pacific Islander men. Although numerous of studies have tried to explain the issue with genetic and molecular approach, the findings for these racial differences are complex and inconsistent.

Family History: Positive family history of prostate cancer is one of the most recognized risk factors for prostate cancer, supporting the presence of a genetic component to the disease. Studies have consistently reported familial aggregation of prostate cancer, showing a 2- to 3- fold increased disease risk among those with first-degree relative with a history of prostate cancer [18, 30]. A large twin study suggest that about 42% (95% CI: 29%-50%) of the risk of prostate cancer may be accounted for by genetic factors [7]. From 5% to 10% of prostate cancer cases are believed to be primarily caused by high-risk inherited genetic factors of prostate cancer susceptibility genes [31].

Dietary Factors

Multiple observational studies attempted to elucidate the association between diet and nutrition with prostate cancer, yet no definitive answers have emerged. A Western diet pattern

has been proposed as a potential risk factor [32], supported by the fact that there is wide variation in prostate cancer incidence rates between population groups. Also, results from migrant studies show higher disease risk among migrants moving from low- to high-risk geographic areas, as well as their offspring. Both observations suggest strong environmental factors are involved. Several food groups and food constituents have been proposed to be protective against prostate cancer, including tomatoes/lycopene, carotenoids, cruciferous vegetables, vitamin E, vitamin D, selenium, fish/marine omega-3 fatty acids, soy, isoflavones and polyphenols; while fat intake (from meat and dairy products), calcium, zinc at high doses and heterocyclic amines may increase risk [33, 34]. However, the conclusion is not firm. A peer-review of 17 studies found suggestive but inconsistent results of association between fatty fish with reduced prostate cancer risk [35]. The measurement error inherent in dietary assessment instruments and laboratory analyses may obscure findings and their interpretation becomes dubious. Cohort studies often fail to account for changing exposure over time; case-control studies are susceptible to recall bias. It is also possible that early life exposures may have a greater impacts on prostate cancer development, while diet may not related with prostate cancer at all. Still, the work concerning diet and prostate cancer has provided crucial clues and can guide future investigations.

Lifestyle Factors

Tobacco Smoking and Prostate Cancer

Smoking is a major preventable cause of premature death and diseases worldwide. Globally, approximately 5.4 million people die each year due to tobacco-related illness. Although cigarette smoke is known to contain multiple carcinogens, and to be associated with multiple cancer sites, the role of cigarette smoking on prostate cancer is not clear. So far, epidemiologic studies have not supported a causal relationship between smoking and total prostate cancer

incidence [36, 37]. Until 1996, the majority of case-control studies (both population- and hospital-based) and cohort studies have reported null associations with several different measures of smoking: current/former/never smoking, number of cigarettes per day, number of years of smoking, age of first cigarettes, and years since quitting [37, 38]. While in 2010, a meta-analysis of 24 prospective cohort studies was conducted to review smoking and risk of prostate cancer: current smokers had no increased risk of incident prostate cancer (21,579 cases; RR=1.04; 95% CI:0.87, 1.24), while after stratification by amount of cigarettes they smoked, elevated risk has been noted with increasing number of cigarettes per day or pack-years of smoking (>20 cigarettes per day: RR=1.22; 95% CI:1.01, 1.46; >21 pack years of smoking: RR=1.11; 95% CI:1.01, 1.22); increased risk was also found among former smokers (RR=1.09; 95% CI:1.02, 1.16) [39]. Nevertheless, these studies cannot convincingly demonstrate causal relationship between smoking and incidence of prostate cancer. The broad, non-quantitative measure of exposure, especially among former smokers might underestimate the strength of the true underlying association, nor did they exclude the confounding influence of other lifestyle risk factors. Smokers are known to consume fewer vegetables and more red meat, factors that are possibly related to prostate cancer risk [40].

The association between smoking and prostate cancer mortality has been documented more consistently. In 1990s, several cohort studies have established an association between smoking and development of fatal prostate cancer. Cigarettes smokers are estimated to be up to twice as likely as nonsmokers to die from prostate cancer [41-44]. The previous meta-analysis found current smokers had an increased risk of fatal prostate cancer (RR=1.14; 95% CI: 1.06, 1.19) [39]. Compared to nonsmokers, the heaviest smokers appeared to have a 24% to 30% greater risk of death from prostate cancer [39]. The association between smoking and prostate cancer is biologically plausible as supported by several studies in humans [45, 46]. Dai et al. suggested that

smoking may modulate the endocrine system by increasing circulating level of testosterone or of the adrenal androgen androstenedione. The elevated levels of circulating androsterone and testosterone among male smokers may increase risk or accelerate cancer progression [46]. Other possible mechanisms include: smoking increasing serum estrogen metabolites that have been postulated to induce a more aggressive tumor phenotype and thereby increase prostate cancer death [47]; smoking causing the mutation of *p53* tumor suppressor gene, creating another pathway to an aggressive tumor phenotype and increased mortality [44]. Besides, the association between smoking and prostate cancer could be modified by BMI. Lean smokers ($\text{BMI} \leq 25 \text{ kg/m}^2$) have an increased risk of developing high-grade prostate cancer ($\text{OR}=2.45$, $\text{P}=0.002$) [48]. These findings suggest the complexity of epidemiological studies of prostate cancer. Further investigation should collect data on smoking history with various measurements, including quantity smoked.

Alcohol drinking and Prostate cancer

Excessive alcohol use has both short-term and long-term risk to human's health. Alcohol drinking was shown to be associated with cancers of the upper aerodigestive tract, female breast, liver, and colorectum [49]. During the past decade, multiple epidemiologic studies have addressed the role of alcohol drinking as a possible modifiable risk factor for prostate cancer [50, 51]. Biological basis for an association between alcohol and cancer, in general, has been identified. It is plausible that the main metabolite of ethanol, acetaldehyde, can affect cell-membrane integrity, enhance production of free radicals, impair immune function and reduce levels of DNA repair enzymes. In addition, the effects of alcohol might be modified by polymorphisms in genes encoding enzymes for ethanol metabolism, folate metabolism, and DNA repair [50]. However, current evidence indicates that moderate alcohol drinking is not associated with prostate cancer.

A meta-analysis of the dose-risk association between alcohol consumption and prostate cancer risk found a weak positive association between alcohol intake and prostate cancer risk. The overall relative risk for any alcohol drinking compared with non/occasional drinking was 1.06 (95% CI: 1.01, 1.10). However, the relative risks were 1.05 (95% CI: 1.02, 1.08), 1.06 (95% CI: 1.01, 1.11), and 1.08 (95% CI: 0.97, 1.20) for light (≤ 1 drink/day), moderate (>1 to <4 drinks/day), and heavy alcohol drinking (≥ 4 drinks/day), respectively [52]. In a large US cohort study, men who consumed more than five alcoholic drinks per day had similar risk as those who consumed less than one drink per day, after adjusting for age, smoking, race and education (<1 drink/day: RR=1.3, 95% CI: 0.8-2.2; >5 drinks/day: RR=1.1, 95% CI: 0.6-2.0)[53]. This finding has been replicated in 2 other cohort studies [54, 55], while Putnam *et al.* have found an increased risk of prostate cancer among heavy alcohol consumers (>96 grams alcohol per week; RR=3.1, 95% CI: 1.5-6.3), compared to non-users of alcohol [56]. Current evidence is not sufficient to indicate a causal association between alcohol drinking and prostate cancer. However, the previous studies rarely looked at the type of alcoholic beverage, drinking patterns, lifetime exposure to alcohol, and potential interaction with tobacco smoking. Epidemiological research suggests that persons who use both alcohol and tobacco have much greater risk of developing cancers, compared with those who use either alcohol or tobacco alone [57, 58]. Whether the combination of alcohol and tobacco may have an impact on prostate cancer is not clear.

Cadmium level and Prostate cancer

Cadmium (Cd) and its compounds are heavy metallic toxicants that have been largely used in industry until the last decade, and are widely dispersed in the environment. In addition to exposure to cadmium through occupational contact, humans are exposed to cadmium through food and tobacco grown in soil containing cadmium [59]. Historically, prostate cancer was the first cancer identified in association with exposure to cadmium [60]. A systematic review of cohort

studies did not confirm the original findings of high-risk estimates for prostate cancer [61]. The literatures concerning prostate cancer and exposure to cadmium from 1966 to 2002 had inconsistent conclusions: three of four descriptive studies, five of ten case-control studies, and three of eleven cohort studies reported positive associations. The overall evidence of association was either weakly positive or negative, indicating potential exposure misclassification. Meanwhile, animal studies demonstrated that cadmium administration via different routes can induce prostate cancer in rats [62]. The possible explanation may due to the limitation of exposure assessment. The available human studies have limited ability to detect an effect and thus reliance on animal findings strengthens the evidence of an association between cadmium exposure and cancer of the prostate in humans.

CHAPTER 2: MANUSCRIPT CHAPTER

Introduction

Prostate cancer has been the most common diagnosed cancer and the second cause of cancer death in American men [1], its prevention and control have become important public health issues. With an approximately 70-fold difference in incidence have been observed among different population groups [4], and a shift toward higher incidence rates with migration to higher risk countries [53], lifestyle is hypothesized to play a significant role in prostate cancer progression. However, other than age, race, and family history, the precise etiological factors associated with the disease risk have not been identified [4, 18, 63, 64].

Smoking is a major preventable cause of premature death and diseases worldwide, which causes about 5.4 million people die directly or indirectly. The carcinogenic effect of cigarette smoking has been identified in several cancer, while its relationship with prostate cancer has not been fully understood. In a recent meta-analysis of 24 prospective cohort studies, current smoking was not associated with overall prostate cancer risk, however, heavy smokers with more than 20 cigarettes per day were more likely to be diagnosed with fatal prostate cancer, and had a 24% to 30% greater risk of death from prostate cancer, compared with never smokers [39]. While in a review of 24 cohort studies, 5 nested and 36 case-control studies, 51 studies found no association between prostate cancer and smoking [45].

As with smoking, excessive alcohol drinking has both short-term and long-term risk to human's health. Alcohol drinking was identified to have causal effects on upper aerodigestive tract, female breast, liver, and colon rectum cancer incidence[50]. Generally, the carcinogenic effect of alcohol drinking is through the metabolite of alcohol, acetaldehyde, which affect cell-membrane integrity, enhance production of free radicals, impair immune system and reduce

levels of DNA repair enzymes [50]. A meta-analysis of the dose-risk association between alcohol consumption and prostate cancer risk found a weak positive association between alcohol intake and prostate cancer risk. Compared with non-alcohol drinkers, heavy alcohol drinkers had an about 8% greater risk of prostate cancer incidence [52]. However, current evidence is not sufficient to indicate a causal association between alcohol drinking and prostate cancer.

To broaden our knowledge and to explore if smoking and alcohol drinking are associated with higher risk of prostate cancer, we investigated the association between cigarettes smoking, alcohol drinking and prostate cancer risk in a community-based matched case-control study. In addition, we also assessed the associations according to cancer severity with a detailed smoking and alcohol drinking patterns assessment.

Material and Methodology

Participant Population

This community-based case-control study of incident prostate cancer was designed to investigate the association between diet, nutrition, metabolic characteristics, lifestyle factors, and incidence of prostate cancer. The study was conducted in the Piedmont Triad area of North Carolina, and was approved by the Committee for Human Research at Wake Forest University, Winston-Salem, North Carolina. Eligible cases were defined to be black and white men over 50 years old, English speaking, with a confirmed pathology-documented diagnosis of prostate cancer during the study period in area urology and radiation oncology practices within days of diagnosis and studied prior to initiating treatment for the disease. Of 203 prostate cancer patients who were initially found to be eligible, 91 were excluded due to the following: 70 (34.5%) refused or did not respond to the study, 12 (6.0%) were unable to come for the study visit, 8 (4.0%) dropped out or were eventually found not eligible to the study during the visit, and 1 (0.5%) did not provide any information on smoking and/or alcohol consumption.

All 113 cases included in the study were newly diagnosed with first time ever prostate cancer and received no treatment for the disease. As with cases, we contacted 877 eligible control subjects. Only 258 (29.4%) completed interview. A total of 584 (66.6%) control subjects refused or did not respond to the study, 35 (4.0%) failed to pass further eligibility assessment during the visit. Among 258 controls completed interview, 3 (1.2%) were excluded from the final analysis due to missing response on smoking and/or alcohol consumption questions. During the study period, 258 controls were recruited from the same geographic area as cases. Community control subjects were frequency 2:1 matched to cases on age and race, and had no history of prostate cancer. In addition, participants were excluded if they had any following conditions: history of previous cancer (other than non-melanoma skin cancer), current prostate diseases (e.g., symptomatic

benign prostatic hypertrophy or prostatitis), previous prostate surgery, active tuberculosis, or current liver or kidney diseases. To identify each control subject, the Polk directory was employed with a random selection procedure.

Data Collection

All participants were required to attend a four- to five-hour study visit at the General Clinical Research Center (GCRC) at Wake Forest University. The visit included informed consent form, in-person interview, a medical/lifestyle questionnaire and a Block Food Frequency Questionnaire, anthropometrics. In addition, participants had to provide blood and spot and timed urine samples. Tobacco smoking was measured by self-report *via* the medical/lifestyle questionnaire with response to relevant questions. Similarly, the measurement towards alcohol drinking combined medical/lifestyle questionnaire response, and food frequency questionnaire. Tumor stages and grades from the TNM system and pathology information on cases were collected from hospital tumor registries.

Statistical Analysis

Participants were defined as regular smokers if they reported had ever been a regular cigarette smoker (defined as more than 100 cigarettes in one's lifetime). If the answer was 'Yes', they then were asked about detailed smoking habits, or they were deemed as non-smokers. Duration of smoking was defined as <10, 10-25, 25+ years; time since quit smoking as <10, 10-20, 20-30 and 30+ years ago if any former smoking habits have been reported; the categorization of smoking intensity was based on number of cigarettes smoked per day as <10 (< half a pack), 10-20 (up to 1 pack) and 20+ (more than 1 pack) as previously described [47, 65]. Similarly, participants were defined as regular alcohol drinkers if they reported had ever been a regular alcohol drinker (defined as more than 100 alcoholic beverage drinks in one's lifetime, including

cans/bottles of beer, glasses of wine, shots of liquor). If participants answered 'Yes', then they were asked about drinking status at the study visit. Cumulative alcohol consumption was expressed in years of drinking as ≤ 20 , 20-40, 40+ years among former drinkers, and ≤ 40 , 40-50, 50+ years among current drinkers as previously described [66], and drinking intensity was defined as number of alcoholic drinks per day as ≤ 1 , 1-2, 2+ standard drinks (one standard drink was 12 oz of beer, 4 oz of wine, or 1.5 oz of liquor) [67, 68].

Tumors were classified as localized (TNM stage O, I, II, or PSA <20 ng/mL, n=68) or advanced (stage III, IV; n=32). Also, tumors were divided into low-histological grade (cases coded as well or moderately differentiated; n=88) or high grade (cases coded as poorly differentiated or undifferentiated; n=14).

Logistic regression was used to examine individual and joint association of smoking status, smoking intensity, duration of smoking, and time since quit, drinking status, drinking intensity (among participants reported as current drinkers), duration of drinking, and time since quit drinking. Analyses were conducted separately for former and current smokers, former and current drinkers. Unadjusted logistic regression was performed to assess the individual association between each exposure of interest and risk of prostate cancer controlling for matching variables (age and race). The multivariable models were generated after checking for collinearity. The models were adjusted for matching variables (age and race), education (11th grade or less, high school or vocational school, college or post graduate), physical activity (vigorous, moderate or less, missing), family history of prostate cancer within first degree relatives (none, ≥ 1 relative, missing), history of vasectomy (none, yes, missing) and prostate-specific antigen (PSA) test (no, yes, missing). Additional adjustment for BMI, history of circumcision, intake of energy, and multivitamin use did not change the effect estimates as assessed by the 10% criteria for evaluating confounding. In the event of quasi-separability in the model or small sample size, Firth's penalized

likelihood approach was employed [69] In addition, we tested for potential effect modifications (on a multiplicative scale) by including cross-product terms of age, race, education, physical activity, family history, PSA test and history of vasectomy along with primary exposure variables in the multivariable model. The likelihood ratio test was used to evaluate the statistical significance of the cross-product terms. Tests for trends were conducted using ordinal scores for categories of smoking/drinking intensity, smoking/drinking duration, and years since quit smoking/drinking. The same models were performed to assess the association of smoking or drinking status with different prostate cancer stages. Both case groups (localized and advanced) were compared to all controls. The criteria for statistical significance was 0.05 for all analyses. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Table 1 summarizes demographic and other lifestyle characteristics of study participants. Family history of prostate cancer in a first degree relative was more common among cases ($p=0.001$). Cases were more likely to report smoking 1-10 cigarettes per day, while controls were more likely to report smoking ≥ 11 cigarettes per day ($p=0.049$). Among former and current smokers, light cigarettes smoking (1-10 cigarettes per day) was more commonly found in cases than in controls (16.5% and 6.7%, respectively). No meaningful differences were detected for other types of tobacco products consumption. Among those who reported drinking regularly, more than half of participants in both case and control groups were light alcohol drinkers. The alcohol drinking patterns did not show any significant difference by case-control status. However, among the three most commonly consumed alcohol beverage types (beer, wine, and liquor), participants were more likely to report alcohol drinking from at least two types.

Among the 112 cases, 102 had histological adenocarcinoma of prostate with TNM stage and tumor grade available. Of 102 cases, 68 (66.7%) had localized disease, 31 (31.4%) advanced

disease, and 2 unknown disease status. Similarly, of 112 tumors, 7 (6.25%) were well differentiated, 81 (72.3%) were moderately differentiated, and 14 (12.5%) were poorly differentiated or undifferentiated.

Smoking Status, Intensity, and Duration

Neither smoking nor alcohol drinking were associated with risk for prostate cancer overall or by tumor severity (Tables 2-5). Current smokers had a statistically non-significant higher risk of prostate cancer than never smokers (crude: $OR_{overall} = 1.44$, 95% CI: 0.66-3.14, Table 2; and multivariable: $OR_{overall} = 1.54$, 95% CI: 0.62-3.82, Table 4). This positive association was more evident for advanced disease (crude: $OR_{advanced} = 2.23$, 95% CI: 0.67-7.45, Table 2; multivariable: $OR_{advanced} = 1.97$, 95% CI: 0.56-6.93, Table 4); however the sample size was small for tumor subtype analysis. Among current smokers, smoking intensity was associated with a non-significant increased risk of prostate cancer compared with never smokers. The multivariable adjusted ORs with 95% CI for three smoking intensity groups were 2.33 (95% CI: 0.24-22.30), 2.60 (95% CI: 0.52-13.09), 1.83 (95% CI: 0.53-6.36), respectively (p-trend: 0.200). Among former smokers, smoking intensity and smoking duration were weakly inversely associated with prostate cancer, with similar associations observed for localized and advanced disease. Former smokers who had smoked at least 25 years had a decreased risk of localized prostate cancer compared with never smokers (crude: $OR_{localized} = 0.37$, 95% CI: 0.16-0.87; multivariable: $OR = 0.41$, 95% CI: 0.17-0.96). The tests for trend were statistically significant in both crude and adjusted models ($p = 0.025$ and $p = 0.046$, respectively). Also, men who had recently, that is, <5 years before recruitment, quit smoking had a statistically non-significant higher risk of both localized and advanced diseases compared to never smokers, and the tests for trend were not statistically significant (Tables 2 and 4). No other smoking patterns were found to be associated with disease risk.

Alcohol Drinking Status and Duration

As shown in Tables 3 and 5, the overall disease risk was higher among former alcohol drinkers compared with never drinkers, and such association was also observed in localized and advanced diseases (crude: $OR_{\text{localized}}=1.77$, 95% CI: 0.90-3.50; $OR_{\text{advanced}}=1.45$, 95% CI: 0.50-4.20; multivariable: $OR_{\text{localized}}=1.61$, 95% CI: 0.75-3.47; $OR_{\text{advanced}}=1.55$, 95% CI: 0.54-4.47). Among former drinkers, compared to never drinkers, those who drank alcohol for <20 years were at higher risk of developing prostate cancer ($OR_{\text{overall}}=2.08$, 95% CI: 0.61-7.18). The association was somewhat stronger for localized disease ($OR_{\text{localized}}=2.75$, 95% CI: 0.73-10.32). Former drinkers who drank for 20-40 and ≥ 40 years, compared to never drinkers, were also at higher risk for developing localized prostate cancer (multivariable $OR_{\text{localized}}=1.91$, 95% CI: 0.67-5.45; $OR_{\text{localized}}=1.74$, 95% CI: 0.48-6.35, respectively). A relative weak decrease in disease risk had been found with years of quitting drinking among former alcohol drinkers. Compared to never drinkers, those who quit < 5 years before being recruited in the study were at a statistically non-significant higher risk of developing prostate cancer (multivariable $OR_{\text{overall}}=1.95$, 95% CI: 0.58-6.58). The association was stronger, but not statistically significant, for localized disease (multivariable $OR_{\text{localized}}=2.11$, 95% CI: 0.54-8.28). Former drinkers who quit 5-15 and ≥ 15 year were also at higher risk of developing the disease (multivariable $OR_{\text{overall}}=1.12$, 95% CI: 0.35-3.58; $OR_{\text{localized}}=1.76$, 95% CI: 0.49-6.35; and $OR_{\text{overall}}=1.58$, 95% CI: 0.62-4.00; $OR_{\text{localized}}=1.94$, 95% CI: 0.70-5.39, respectively). Current drinkers of up to 1 standard drink per day had a higher disease risk compared with non-drinkers (crude: $OR_{\text{overall}}=2.51$, 95% CI: 0.89-7.14; multivariable: $OR_{\text{overall}}=1.32$, 95% CI: 0.42-4.16), but the association was inversed both in moderate and heavy alcohol consumption (crude: $OR_{\text{overall}}=0.68$, 95% CI: 0.13-3.51; $OR_{\text{overall}}=0.61$, 95% CI: 0.14-3.64; multivariable: $OR_{\text{overall}}=0.45$, 95% CI: 0.09-2.38; $OR_{\text{overall}}=0.69$, 95% CI: 0.15-3.18). No other meaningful associations with

prostate cancer risk were found among current drinkers with their alcoholic beverage consumption.

Discussion

In this case-control study, neither tobacco smoking nor alcohol consumption were associated with prostate cancer risk; however, there was a suggestion for a possible inverse association between smoking duration and less aggressive incident disease among former smokers.

Numerous observational studies have been conducted to investigate whether smoking and/or alcohol drinking are associated with prostate cancer risk. With 23 prospective and 1 retrospective cohorts, 5 nested/prospective and 36 traditional/retrospective case-control studies having looked at the prostate cancer-smoking association, 11 studies found positive association, 3 studies found inverse association, and the rest 51 studies found no association between prostate cancer and smoking [45]. The possible reasons for the previous inconsistent results could be the failure to separate former smokers from either never or current smokers, the definition of smoking status was obscure, or smoking status of study subjects was not updated despite quite long follow-up periods, which could bias the effect estimate towards the null. In the current study, current smokers had a statistically non-significant 54% higher risk of prostate cancer compared to never smokers. An inverse association of smoking duration with overall disease risk among former smokers has been suggested, with the results being statistically significant among localized cases. A similar inverse association between former smoking and localized prostate cancer has been reported in other studies [47, 70, 71]. As noted in a large cohort study, former smoking was associated with decreased risk of non-advanced prostate cancer (HR=0.82, 95% CI: 0.86-0.92) [71]. The inverted association may reflect a report bias, such that former smokers are not willing to report, or underestimate their cigarette consumption and therefore may not be identified as

regular smokers, or equally likely participants may underestimate their cigarettes usage which may then be defined as light smokers. In addition, detection bias can contribute too. Former smokers may be less likely to be health conscious and undergo medical tests, thus they are less likely to be diagnosed with prostate cancer. More than 40% of former smokers in the control group reported not ever taking prostate cancer testing, and thus, may miss some cancer cases. Another possible explanation for the inverse association has been presented in the NIH-AARP cohort [71]. Watters *et al.* speculated that the inverse association between smoking and localized prostate cancer incidence might partly be explained by effects of smoking on circulating levels of insulin-like growth factor (IGF) and sex hormone-binding globulin. Higher concentrations of IGF-I are associated with a moderately increased risk for prostate cancer [72], while lower levels of IGF-I have been found with increasing cigarette use among current smokers [73]. Smokers with shorter but most recent smoking history might have relative low level of IGF-I compared to those with longer smoking history, which may protect them from a less aggressive disease. However, further studies are needed to clarify the true association between smoking and localized prostate cancer.

We found that former alcohol drinkers had a slightly higher risk for prostate cancer, but the association was not statistically significant. Current alcohol consumption was not associated with prostate cancer risk, which was consistent with findings from previous studies [52, 54, 74]. As Rota *et al.* concluded from a comprehensive meta-analysis, no evidence were shown that alcohol drinking had a material association with prostate cancer risk (ref). In current study, current alcohol consumption did not increase prostate cancer risk; while an about 1.5- to 2-fold increase of risk has been detected among participants with former alcohol consumption; however these results were not statistically significant. As noted in another study, about a 2-fold increase in risk has been found among heavy alcohol consumption and regular heavy drinking [75]. It is possible

that some former alcohol drinkers in our study were heavy alcohol drinkers and quit drinking after the disease diagnosis. The findings of higher disease risk among former drinkers can be supported with biological plausibility. Gong *et al.* speculated that alcohol might affect the metabolism of carcinogens and suppress DNA repair; increase DNA damage due to excess oxidative stress, impair immune response and increase risk of micronutrients deficiencies caused by alcohol consumption [75]. On the other hand, Mucci *et al.* found that alcohol intake appeared to reduce serum IGF-I levels, with which the effect although modest, was statistically significant [76]. If true, then increased alcohol drinking may act as a protective factor for prostate cancer. Both hypotheses implicate an effect of alcohol drinking on disease progression. However, our findings do not have enough evidence to support either hypotheses. Further studies are needed to clarify the true association and most possible biological mechanisms.

This study has several strengths and limitations. One strength that is also a limitation is that the in-person data collection procedures ensured high quality information, but because of being time-consuming, they differentially affected the consent rates (55.7% among cases and 29.4% among controls), which potentially might bias the results. Since the data collection procedures required 4-5 hours study visit with multiple questionnaires, the response rate was lower among controls. It is possible that men who refused to participate were less health-conscious or differed from those who agree to participate on a number of lifestyle and other risk factors, and they may have higher disease risk compared to those who completed the procedures. Another strength of the study was the community-based design and that all cases were newly diagnosed before any initiation of treatment. As most case-control studies, this study has limitations, including possible recall bias. The misreport of tobacco and alcohol consumption among cases would likely bias associations toward the null. A further limitation is that no prostate cancer test or biopsies were conducted on controls to rule out any sub-clinical prostate cancer

and to reduce possible misclassification. If some controls had prostate cancer but had not been detected, our results would have been biased toward the null. Another limitation was the relative small sample size, which restricted our ability to investigate interactions by stratified analyses. After further classification of smoking/drinking patterns, some categories had less than 5 cases, which affected statistical power. In addition, smoking was shown to be associated with chronic prostatic inflammation [77], while chronic prostatic inflammation may initiate and promote prostate cancer development [78]. Some former or current smokers in the control group may have prostatic inflammation but have not developed the disease yet. Then people who smoke are more likely to have prostatic inflammation, which may develop into prostate cancer.

In conclusion, in conflict with our original hypothesis that smoking and/or alcohol drinking are associated with higher prostate cancer risk, our study found no evidence for an association between risk of incident prostate cancer and tobacco smoking or alcohol consumption.

Chapter 3: Conclusions

Summary

We did not find smoking or alcohol drinking to be significantly associated with the risk of incident prostate cancer. After multivariable adjustment, there was a suggestion for a possible inverse association between smoking duration and less aggressive incident disease among former smokers, with statistically significant p-trend; but the sample size was relatively small. These findings suggest that smoking and alcohol drinking are not risk factors for prostate cancer.

Our results suggested that former smokers with ≥ 25 years of smoking history might be at lower risk for prostate cancer; however the sample was small for this analysis. Although the biological plausibility of the association between smoking and lower IGF-1 levels may support the finding, the failure of noting a similar trend among current smokers indicate that this may have been due to a report bias or chance.

Public Health Implications

Our findings have several public health implications. As prostate cancer is the most diagnosed malignant disease in the USA and Canada, with a gradual increase in the incidence in South America, Asia and Europe [79], its prevention and control are becoming increasingly important as public health issues for chronic disease. Due to large global incidence variation and findings from migration studies [4, 5], identifying modifiable lifestyle factors could contribute to successful cancer prevention strategies. Smoking and alcohol drinking, the most common modifiable lifestyle risk factors for chronic diseases, have been identified to play an important role in the etiology of several cancers [49, 80-82]. However, our and previously published epidemiologic studies found that neither smoking nor alcohol drinking is associated with prostate

cancer risk. The inconsistent results reflect difficulties in cancer risk assessment. In our analyses, an inverse association has been suggested among former smokers with ≥ 25 years smoking history and localized prostate cancer. The finding might be explained by a possible protective effect of smoking on IGF-1 levels, which are hypothesized to contribute to prostate cancer development; however, further studies are required to understand possible biological mechanisms.

Abbreviations

HPC = Heredity prostate cancer

BMI = Body mass index

OR = Odds ratio

CI = Confidence interval

IGF = Insulin-like Growth Factor

Reference

1. Society, A.C., *Cancer facts & figures*. 2014.
2. Jemal, A., et al., *Global cancer statistics*. CA Cancer J Clin, 2011. **61**(2): p. 69-90.
3. Muir, C.S., et al, *Cancer incidence in five continents*. V. IARC scientific publication, 1987.
4. Gronberg, H., *Prostate cancer epidemiology*. Lancet, 2003. **361**(9360): p. 859-64.
5. Shimizu, *Cancers of the prostate and breast among Japanese and white immigrants in Los Angeles County*. Br.J Cancer, 1991. **63**.6: p. 963.
6. Baker, S.G., et al., *Genetic susceptibility to prostate, breast, and colorectal cancer among Nordic twins*. Biometrics, 2005. **61**(1): p. 55-63.
7. Lichtenstein, P., et al., *Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland*. N Engl J Med, 2000. **343**(2): p. 78-85.
8. Bratt, O., et al., *Familial and hereditary prostate cancer in southern Sweden. A population-based case-control study*. Eur J Cancer, 1999. **35**(2): p. 272-7.
9. Lesko, S.M., L. Rosenberg, and S. Shapiro, *Family history and prostate cancer risk*. Am J Epidemiol, 1996. **144**(11): p. 1041-7.
10. Cerhan, J.R., et al., *Family history and prostate cancer risk in a population-based cohort of Iowa men*. Cancer Epidemiol Biomarkers Prev, 1999. **8**(1): p. 53-60.
11. Schuurman, A.G., et al., *A case-cohort study on prostate cancer risk in relation to family history of prostate cancer*. Epidemiology, 1999. **10**(2): p. 192-5.
12. Monroe, K.R., et al., *Evidence of an X-linked or recessive genetic component to prostate cancer risk*. Nat Med, 1995. **1**(8): p. 827-9.
13. Xu, J., et al., *Evidence for a prostate cancer susceptibility locus on the X chromosome*. Nat Genet, 1998. **20**(2): p. 175-9.
14. Kote-Jarai, Z., et al., *Seven prostate cancer susceptibility loci identified by a multi-stage genome-wide association study*. Nat Genet, 2011. **43**(8): p. 785-91.
15. Amundadottir, L.T., et al., *A common variant associated with prostate cancer in European and African populations*. Nat Genet, 2006. **38**(6): p. 652-8.
16. Kim, S.T., et al., *Prostate cancer risk-associated variants reported from genome-wide association studies: meta-analysis and their contribution to genetic Variation*. Prostate, 2010. **70**(16): p. 1729-38.
17. Chung, C.C., et al., *A comprehensive resequence-analysis of 250 kb region of 8q24.21 in men of African ancestry*. Prostate, 2014. **74**(6): p. 579-89.
18. Hsing, A.W. and A.P. Chokkalingam, *Prostate cancer epidemiology*. Front Biosci, 2006. **11**: p. 1388-413.
19. Ingles, S.A., et al., *Association of prostate cancer risk with genetic polymorphisms in vitamin D receptor and androgen receptor*. J Natl Cancer Inst, 1997. **89**(2): p. 166-70.
20. Yoo, S., et al., *Androgen receptor CAG repeat polymorphism and risk of TMPRSS2:ERG-positive prostate cancer*. Cancer Epidemiol Biomarkers Prev, 2014. **23**(10): p. 2027-31.
21. Sartor, O., Q. Zheng, and J.A. Eastham, *Androgen receptor gene CAG repeat length varies in a race-specific fashion in men without prostate cancer*. Urology, 1999. **53**(2): p. 378-80.
22. Huggins, C. and C.V. Hodges, *Studies on prostatic cancer: I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate*. 1941. J Urol, 2002. **168**(1): p. 9-12.
23. Jin, J.K., F. Dayyani, and G.E. Gallick, *Steps in prostate cancer progression that lead to bone metastasis*. Int J Cancer, 2011. **128**(11): p. 2545-61.

24. Feldman, B.J. and D. Feldman, *The development of androgen-independent prostate cancer*. Nat Rev Cancer, 2001. **1**(1): p. 34-45.
25. Dutt, S.S. and A.C. Gao, *Molecular mechanisms of castration-resistant prostate cancer progression*. Future Oncol, 2009. **5**(9): p. 1403-13.
26. Lou, W., et al., *Interleukin-6 induces prostate cancer cell growth accompanied by activation of stat3 signaling pathway*. Prostate, 2000. **42**(3): p. 239-42.
27. Chen, T., L.H. Wang, and W.L. Farrar, *Interleukin 6 activates androgen receptor-mediated gene expression through a signal transducer and activator of transcription 3-dependent pathway in LNCaP prostate cancer cells*. Cancer Res, 2000. **60**(8): p. 2132-5.
28. Foundation, P.C., *Prostate Cancer Risk Factors*, 2014.
29. Jemal, A., et al., *Cancer statistics, 2007*. CA Cancer J Clin, 2007. **57**(1): p. 43-66.
30. Stanford, J.L. and E.A. Ostrander, *Familial prostate cancer*. Epidemiol Rev, 2001. **23**(1): p. 19-23.
31. Bratt, O., *Hereditary prostate cancer: clinical aspects*. J Urol, 2002. **168**(3): p. 906-13.
32. Hebert, J.R., et al., *Nutritional and socioeconomic factors in relation to prostate cancer mortality: a cross-national study*. J Natl Cancer Inst, 1998. **90**(21): p. 1637-47.
33. Chan, J.M., P.H. Gann, and E.L. Giovannucci, *Role of diet in prostate cancer development and progression*. J Clin Oncol, 2005. **23**(32): p. 8152-60.
34. Giovannucci, E., *Does prostate-specific antigen screening influence the results of studies of tomatoes, lycopene, and prostate cancer risk?* J Natl Cancer Inst, 2007. **99**(14): p. 1060-2.
35. Terry, P.D., T.E. Rohan, and A. Wolk, *Intakes of fish and marine fatty acids and the risks of cancers of the breast and prostate and of other hormone-related cancers: a review of the epidemiologic evidence*. Am J Clin Nutr, 2003. **77**(3): p. 532-43.
36. Colditz, G., *Consensus conference: smoking and prostate cancer*. Cancer Causes Control, 1996. **7**(5): p. 560-2.
37. Lumey, L.H., *Prostate cancer and smoking: a review of case-control and cohort studies*. Prostate, 1996. **29**(4): p. 249-60.
38. Lumey, L.H., et al., *Cigarette smoking and prostate cancer: no relation with six measures of lifetime smoking habits in a large case-control study among U.S. whites*. Prostate, 1997. **33**(3): p. 195-200.
39. Huncharek, M., et al., *Smoking as a risk factor for prostate cancer: a meta-analysis of 24 prospective cohort studies*. Am J Public Health, 2010. **100**(4): p. 693-701.
40. Key, T.J., et al., *Diet, nutrition and the prevention of cancer*. Public Health Nutr, 2004. **7**(1A): p. 187-200.
41. Hsing, A.W., et al., *Diet, tobacco use, and fatal prostate cancer: results from the Lutheran Brotherhood Cohort Study*. Cancer Res, 1990. **50**(21): p. 6836-40.
42. Coughlin, S.S., J.D. Neaton, and A. Sengupta, *Cigarette smoking as a predictor of death from prostate cancer in 348,874 men screened for the Multiple Risk Factor Intervention Trial*. Am J Epidemiol, 1996. **143**(10): p. 1002-6.
43. Rodriguez, C., et al., *Smoking and fatal prostate cancer in a large cohort of adult men*. Am J Epidemiol, 1997. **145**(5): p. 466-75.
44. Giovannucci, E., et al., *Smoking and risk of total and fatal prostate cancer in United States health professionals*. Cancer Epidemiol Biomarkers Prev, 1999. **8**(4 Pt 1): p. 277-82.
45. Hickey, K., K.A. Do, and A. Green, *Smoking and prostate cancer*. Epidemiol Rev, 2001. **23**(1): p. 115-25.

46. Dai, W.S., et al., *Cigarette smoking and serum sex hormones in men*. Am J Epidemiol, 1988. **128**(4): p. 796-805.
47. Rohrmann, S., et al., *Smoking and the risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition*. Br J Cancer, 2013. **108**(3): p. 708-14.
48. Ho, T., et al., *Smoking and Risk of Low- and High-Grade Prostate Cancer: Results from the REDUCE Study*. Clin Cancer Res, 2014. **20**(20): p. 5331-8.
49. Baan, R., et al., *Carcinogenicity of alcoholic beverages*. Lancet Oncol, 2007. **8**(4): p. 292-3.
50. Boffetta, P. and M. Hashibe, *Alcohol and cancer*. Lancet Oncol, 2006. **7**(2): p. 149-56.
51. Dennis, L.K., *Meta-analysis for combining relative risks of alcohol consumption and prostate cancer*. Prostate, 2000. **42**(1): p. 56-66.
52. Rota, M., et al., *Alcohol consumption and prostate cancer risk: a meta-analysis of the dose-risk relation*. Eur J Cancer Prev, 2012. **21**(4): p. 350-9.
53. Hiatt, R.A., et al., *Alcohol consumption, smoking, and other risk factors and prostate cancer in a large health plan cohort in California (United States)*. Cancer Causes Control, 1994. **5**(1): p. 66-72.
54. Platz, E.A., et al., *Alcohol intake, drinking patterns, and risk of prostate cancer in a large prospective cohort study*. Am J Epidemiol, 2004. **159**(5): p. 444-53.
55. Baglietto, L., et al., *Alcohol consumption and prostate cancer risk: results from the Melbourne collaborative cohort study*. Int J Cancer, 2006. **119**(6): p. 1501-4.
56. Putnam, S.D., et al., *Lifestyle and anthropometric risk factors for prostate cancer in a cohort of Iowa men*. Ann Epidemiol, 2000. **10**(6): p. 361-9.
57. Hashibe, M., et al., *Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium*. Cancer Epidemiol Biomarkers Prev, 2009. **18**(2): p. 541-50.
58. Turati, F., et al., *A meta-analysis of alcohol drinking and oral and pharyngeal cancers: results from subgroup analyses*. Alcohol Alcohol, 2013. **48**(1): p. 107-18.
59. Adams, S.V. and P.A. Newcomb, *Cadmium blood and urine concentrations as measures of exposure: NHANES 1999-2010*. J Expo Sci Environ Epidemiol, 2014. **24**(2): p. 163-70.
60. Lemen, R.A., et al., *Cancer mortality among cadmium production workers*. Ann N Y Acad Sci, 1976. **271**: p. 273-9.
61. Verougstraete, V., D. Lison, and P. Hotz, *Cadmium, lung and prostate cancer: a systematic review of recent epidemiological data*. J Toxicol Environ Health B Crit Rev, 2003. **6**(3): p. 227-55.
62. Waalkes, M.P., et al., *Cadmium carcinogenesis in male Wistar [Crl:(WI)BR] rats: dose-response analysis of tumor induction in the prostate and testes and at the injection site*. Cancer Res, 1988. **48**(16): p. 4656-63.
63. Bai, Y., et al., *Risk of prostate cancer and family history of cancer: a population-based study in China*. Prostate Cancer Prostatic Dis, 2005. **8**(1): p. 60-5.
64. Ghadirian, P., et al., *Family history of prostate cancer: a multi-center case-control study in Canada*. Int J Cancer, 1997. **70**(6): p. 679-81.
65. Okuyemi, K.S., J.S. Ahluwalia, and W.C. Wadland, *The evaluation and treatment of tobacco use disorder*. J Fam Pract, 2001. **50**(11): p. 981-7.
66. Castellsague, X., et al., *Independent and joint effects of tobacco smoking and alcohol drinking on the risk of esophageal cancer in men and women*. Int J Cancer, 1999. **82**(5): p. 657-64.
67. *Dietary Guidelines for Americans*. 2010.
68. *CDC Alcohol and Public Health*. 2014.

69. Heinze, G. and M. Ploner, *Fixing the nonconvergence bug in logistic regression with SPLUS and SAS*. *Comput Methods Programs Biomed*, 2003. **71**(2): p. 181-7.
70. Giovannucci, E., et al., *Risk factors for prostate cancer incidence and progression in the health professionals follow-up study*. *Int J Cancer*, 2007. **121**(7): p. 1571-8.
71. Watters, J.L., et al., *Cigarette smoking and prostate cancer in a prospective US cohort study*. *Cancer Epidemiol Biomarkers Prev*, 2009. **18**(9): p. 2427-35.
72. Roddam, A.W., et al., *Insulin-like growth factors, their binding proteins, and prostate cancer risk: analysis of individual patient data from 12 prospective studies*. *Ann Intern Med*, 2008. **149**(7): p. 461-71, W83-8.
73. Renehan, A.G., et al., *The effect of cigarette smoking use and cessation on serum insulin-like growth factors*. *Br J Cancer*, 2004. **91**(8): p. 1525-31.
74. Schoonen, W.M., et al., *Alcohol consumption and risk of prostate cancer in middle-aged men*. *Int J Cancer*, 2005. **113**(1): p. 133-40.
75. Gong, Z., et al., *Alcohol consumption, finasteride, and prostate cancer risk: results from the Prostate Cancer Prevention Trial*. *Cancer*, 2009. **115**(16): p. 3661-9.
76. Mucci, L.A., et al., *Are dietary influences on the risk of prostate cancer mediated through the insulin-like growth factor system?* *BJU Int*, 2001. **87**(9): p. 814-20.
77. Daniel M. Moreira¹, J.C.N., Leah Gerber^{3,4}, Roberto L. Muller^{3,4}, Gerald L. Andriole⁵, Ramiro Castro-Santamaria⁶ and Stephen J. Freedland, *Smoking is associated with acute and chronic prostatic inflammation: Results from the REDUCE study*. 2015.
78. Nelson, W.G., et al., *The role of inflammation in the pathogenesis of prostate cancer*. *J Urol*, 2004. **172**(5 Pt 2): p. S6-11; discussion S11-2.
79. Quinn, M. and P. Babb, *Patterns and trends in prostate cancer incidence, survival, prevalence and mortality. Part I: international comparisons*. *BJU Int*, 2002. **90**(2): p. 162-73.
80. Boffetta, P., et al., *Risk of cancers of the lung, head and neck in patients hospitalized for alcoholism in Sweden*. *Br J Cancer*, 2001. **85**(5): p. 678-82.
81. Turner, S.A., J.L. Daniels, and J.G. Hollandsworth, *The effects of a multicomponent smoking cessation program with chronic obstructive pulmonary disease outpatients*. *Addict Behav*, 1985. **10**(1): p. 87-90.
82. Matsuda, T. and R. Machii, *Morphological distribution of lung cancer from Cancer Incidence in Five Continents Vol. X*. *Jpn J Clin Oncol*, 2015. **45**(4): p. 404.

Tables

Table 1. Demographic Characteristic of Men Diagnosed with Incident Prostate Cancer and Controls^a, Piedmont Triad Area, North Carolina, U.S., 1994-1996 (n=367)

Characteristic	Case (n=111)	Control ^b (n=254)	p-value*
Age (years)	66.2 (7.47)	66.9 (7.62)	0.437
White	84.7	85.8	0.776
Education (%)			
College	31.5	33.1	0.171
1 st relative with prostate cancer (%)	21.6	15.4	0.002*
Smoking Status (%)			0.420
Never	28.8	28.7	
Former	57.7	62.2	
Current	13.4	9.1	
Smoking Intensity (%), cigarettes per day			0.049*
1-10	16.5	6.7	
11-20	24.1	28.5	
>20	59.5	64.8	
Other Tobacco (%)			
Cigars	2.5	2.2	0.936
Pipe	2.5	2.8	0.521
Snuff	2.5	0.6	0.300
Chew	8.9	5.5	0.507
Alcohol Intake Status (%)			0.354
Never	34.2	35.8	
Former	29.7	22.8	
Current	36.0	41.3	
Type of Alcohol (%)			
Beer	56.2	66.3	0.137
Wine	31.5	38.7	0.292
Liquor	57.5	64.4	0.313
Alcohol Drinking Intensity ^b (%), drink(s) per day			0.191
≥0--1	45.0	38.1	
1-2	17.5	27.6	
>2	27.5	31.4	
Physical Activity Level ^c (%)			0.471
Light	29.7	29.5	
Moderate	54.1	57.5	
Vigorous	14.4	9.5	
BMI, kg/m ²	27.0 (4.0)	27.3 (3.4)	0.431

Vasectomy (%)	23.4	26.0	0.865
History of Circumcision (%)	42.3	44.9	0.548
History of PSA Test (%)	92.8	61.4	<0.0001*
Multivitamin use (%)	69.4	76.4	0.160
Total energy intake (kcal/day)	1939.0 (808.8)	1,898.5 (789.0)	0.655

a: all controls were frequency matched to cases on age and race, without history of prostate cancer;

b: alcohol intensity was rated depending on CDC's classification, and only measured among current alcohol drinkers;

c: activity level was rated as current occupation (former, if retired) physical level;

*: all P-values were two-sided, p-values from Chi-square test (Fisher test if obs≤5) for categorical variables and two-sample t-test for continuous variable;

Table 2. Unadjusted Associations of Smoking Status, Intensity, and Duration with Prostate Cancer Overall and by Tumor Severity

Variable	Total Prostate Cancer			Localized Prostate Cancer		Advanced Prostate Cancer	
	Case (n=111)	Control (n=254)	OR ^b (95% CI)	Case (n=68)	OR ^b (95% CI)	Case (n=31)	OR ^b (95% CI)
Smoking status							
Never smokers	32	73	1.00 (<i>ref.</i>)	20	1.00 (<i>ref.</i>)	7	1.00 (<i>ref.</i>)
Former smokers	64	158	0.93 (0.56, 1.55)	40	0.92 (0.50, 1.68)	17	1.18 (0.46, 3.01)
Current smokers	15	23	1.44 (0.66, 3.14)	8	1.29 (0.50, 3.35)	7	2.23 (0.67, 7.45)
Among former cigarette smokers							
Smoking intensity							
1-10 cigarettes per day	11	10	2.51 (0.97, 6.51)	7	2.56 (0.87, 7.59)	2	2.10 (0.36, 12.34)
11-20 cigarettes per day	15	44	0.79 (0.38, 1.62)	9	0.75 (0.31, 1.79)	5	1.31 (0.38, 4.55)
>20 cigarettes per day	38	102	0.85 (0.49, 1.49)	24	0.85 (0.44, 1.66)	10	1.07 (0.38, 2.99)
<i>P</i> -trend			0.243		0.329		0.857
Duration of smoking							
≥0-<10 years	6	14	1.01 (0.35, 2.87)	6	1.53 (0.52, 4.53)	--	-- ^c
10-25 years	16	40	0.91 (0.45, 1.88)	9	0.81 (0.33, 1.95)	5	1.26 (0.36, 4.36)
≥25 years	22	88	0.57 (0.30, 1.07)	9	0.37 (0.16, 0.87)	9	1.12 (0.39, 3.26)
<i>P</i> -trend			0.047		0.025*		0.318
Years since quit							
≥0-<5 years ago	6	6	2.18 (0.64, 7.35)	2	1.19 (0.22, 6.42)	3	3.61 (0.70, 18.71)
5-15 years ago	14	48	0.65 (0.31, 1.35)	6	0.46 (0.17, 1.22)	7	1.33 (0.42, 4.18)
≥15 years ago	43	100	1.00 (0.58, 1.74)	31	1.14 (0.60, 2.18)	7	0.88 (0.29, 2.67)
<i>P</i> -trend			0.716		0.840		0.729
Among current cigarette smokers							
Smoking intensity							
1-10 cigarettes per day	2	2	3.17 (0.39, 25.73)	1	2.33 (0.18, 29.56)	1	6.07 (0.40, 91.82)
11-20 cigarettes per day	4	7	1.41 (0.37, 5.36)	1	0.48 (0.05, 4.25)	3	4.25 (0.85, 21.24)
>20 cigarettes per day	9	14	1.53 (0.59, 4.01)	6	1.73 (0.57, 5.24)	3	2.05 (0.44, 9.57)
<i>P</i> -trend			0.280		0.506		0.115
Duration of smoking							
≥0-<10 years	--	--	-- ^c	--	-- ^c	--	-- ^c
10-25 years	--	--	-- ^c	--	-- ^c	--	-- ^c
≥10 years	11	20	1.34 (0.56, 3.23)	5	0.97 (0.32, 2.98)	6	2.89 (0.83, 10.15)
<i>P</i> -trend			0.215		0.470		0.078

a: 111 cases have been included in the final analysis;

b: the unadjusted model contains main exposure and matching variables (race and age);
c: There were no cases in this category;

Table 3. Unadjusted Association of Alcohol Drinking Status, Intensity, and Duration with Prostate Cancer Overall and by Tumor Severity

Variable	Total Prostate Cancer			Localized Prostate Cancer		Advanced Prostate Cancer	
	Case (n=111)	Control (n=254)	OR ^b (95% CI)	Case (n=68)	OR ^b (95% CI)	Case (n=31)	OR ^b (95% CI)
Drinking status							
Never drinkers	38	91	1.00 (<i>ref.</i>)	21	1.00 (<i>ref.</i>)	8	1.00 (<i>ref.</i>)
Former drinkers	33	58	1.35 (0.76, 2.40)	23	1.77 (0.90, 3.50)	8	1.45 (0.50, 4.20)
Current drinkers	40	105	0.88 (0.52, 1.49)	24	0.96 (0.50, 1.86)	15	1.38 (0.54, 3.52)
Among former drinkers							
Duration of drinking							
≥0-<20 years	8	12	1.51 (0.57, 4.01)	6	2.03 (0.68, 6.09)	--	-- ^c
20-40 years	14	29	1.22 (0.57, 2.60)	9	1.47 (0.60, 3.65)	5	1.72 (0.50, 5.91)
≥40 years	8	14	1.43 (0.55, 3.72)	7	2.35 (0.83, 6.68)	1	1.08 (0.12, 9.66)
<i>P</i> -trend			0.193		0.176		0.065
Quit drinking							
≥0-<5 years ago	7	9	1.86 (0.64, 5.37)	5	2.53 (0.76, 8.44)	2	2.26 (0.39, 12.95)
5-15 years ago	8	15	1.45 (0.54, 3.85)	4	2.05 (0.68, 6.22)	2	1.13 (0.20, 6.39)
≥15 years ago	15	32	1.11 (0.54, 2.29)	11	1.49 (0.64, 3.46)	2	0.85 (0.17, 4.32)
<i>P</i> -trend			0.341		0.202		0.349
Among current drinkers							
Drinking Intensity							
≥0--1 drink per day	18	40	1.06 (0.54, 2.09)	8	0.87 (0.35, 2.13)	10	2.51 (0.89, 7.14)
1-2 drink per day	7	29	0.57 (0.23, 1.42)	5	0.75 (0.26, 2.16)	2	0.68 (0.13, 3.51)
>2 drink per day	11	33	0.81 (0.36, 1.78)	9	1.18 (0.48, 2.88)	2	0.61 (0.14, 3.64)
<i>P</i> -trend			0.880		0.601		0.756
Duration of drinking							
≥0-<40 years	10	28	0.83 (0.32, 2.12)	5	0.70 (0.21, 2.31)	5	1.18 (0.28, 4.89)
40-50 years	18	42	1.03 (0.52, 2.04)	10	0.98 (0.42, 2.32)	8	2.10 (0.71, 6.23)
≥50 years	12	35	0.83 (0.38, 1.82)	9	1.71 (0.46, 2.97)	2	0.91 (0.17, 4.88)
<i>P</i> -trend			0.717		0.947		0.442

a: 111 cases have been included in the final analysis;

b: the adjusted model contains main exposure, matching variables (race and age);

c: There were no cases in this category.

Table 4. Multivariable Associations of Smoking Status, Intensity, and Duration with Prostate Cancer Overall and by Tumor Severity

Variable	Total Prostate Cancer			Localized Prostate Cancer		Advanced Prostate Cancer	
	Case (n=111)	Control (n=254)	OR ^b (95% CI)	Case (n=68)	OR ^b (95% CI)	Case (n=31)	OR ^b (95% CI)
Smoking status							
Never smokers	32	73	1.00 (<i>ref.</i>)	20	1.00 (<i>ref.</i>)	7	1.00 (<i>ref.</i>)
Former smokers	64	158	0.98 (0.56, 1.73)	40	0.94 (0.49, 1.83)	17	1.17 (0.47, 2.94)
Current smokers	15	23	1.54 (0.62, 3.82)	8	1.37 (0.46, 4.09)	7	1.97 (0.56, 6.93)
Among former cigarette smokers							
Smoking intensity							
1-10 cigarettes per day	11	10	1.84 (0.64, 5.32)	7	2.31 (0.70, 7.56)	2	1.13 (0.19, 6.82)
11-20 cigarettes per day	15	44	0.82 (0.37, 1.84)	9	0.80 (0.30, 2.08)	5	1.05 (0.32, 3.48)
>20 cigarettes per day	38	102	0.93 (0.49, 1.79)	24	1.02 (0.48, 2.16)	10	0.75 (0.26, 2.18)
<i>P</i> -trend			0.541		0.786		0.577
Duration of smoking							
≥0-<10 years	6	14	2.00 (0.61, 6.54)	6	1.66 (0.55, 5.02)	-	-- ^c
10-25 years	16	40	1.16 (0.44, 3.10)	9	0.85 (0.34, 2.14)	5	0.74 (0.19, 2.90)
≥25 years	22	88	0.48 (0.20, 1.16)	9	0.41 (0.17, 0.96)	9	0.87 (0.30, 2.48)
<i>P</i> -trend			0.104		0.046*		0.649
Quit smoking							
≥0-<5 years ago	6	6	2.08 (0.56, 7.68)	2	1.53 (0.27, 8.63)	3	2.97 (0.59, 15.04)
5-15 years ago	14	48	0.62 (0.27, 1.42)	6	0.53 (0.19, 1.46)	7	0.83 (0.26, 2.66)
≥15 years ago	43	100	1.05 (0.56, 2.00)	31	1.34 (0.65, 2.76)	8	0.62 (0.20, 1.91)
<i>P</i> -trend			0.920		0.494		0.270
Among current cigarette smokers							
Smoking intensity							
1-10 cigarettes per day	2	2	2.33 (0.24, 22.30)	1	2.01 (0.11, 37.56)	1	2.71 (0.14, 54.02)
11-20 cigarettes per day	4	7	2.60 (0.52, 13.09)	1	1.81 (0.20, 16.50)	3	3.97 (0.67, 23.44)
>20 cigarettes per day	9	14	1.83 (0.53, 6.36)	6	2.78 (0.63, 12.26)	3	1.42 (0.28, 7.24)
<i>P</i> -trend			0.200		0.186		0.329
Duration of smoking							
≥0-<10 years	--	--	-- ^c	--	-- ^c	-	-- ^c
10-25 years	--	--	-- ^c	--	-- ^c	-	-- ^c
≥10 years	11	20	1.94 (0.64, 5.85)	5	1.89 (0.47, 7.66)	6	2.23 (0.58, 8.50)
<i>P</i> -trend			0.165		0.182		0.286

a: 111 cases have been included in the final analysis;

b: the adjusted model contains main exposure, matching variables (race and age) and potential confounders (family history, physical activity and history of vasectomy);

c: There were no cases in this category.

Table 5. Multivariable-Adjusted Association of Alcohol Drinking Status, Intensity, and Duration with Prostate Cancer Overall and by Tumor Severity

Variable	Total Prostate Cancer			Localized Prostate Cancer		Advanced Prostate Cancer	
	Case (n=111)	Control (n=254)	OR ^b (95% CI)	Case (n=68)	OR ^b (95% CI)	Case (n=32)	OR ^b (95% CI)
Drinking status							
Never drinkers	38	91	1.00 (<i>ref.</i>)	21	1.00 (<i>ref.</i>)	8	1.00 (<i>ref.</i>)
Former drinkers	33	58	1.35 (0.70, 2.63)	23	1.61 (0.75, 3.47)	8	1.55 (0.54, 4.47)
Current drinkers	40	105	0.94 (0.51, 1.73)	24	0.89 (0.43, 1.83)	15	1.40 (0.53, 3.71)
Among former drinkers							
Duration of drinking							
≥0-<20 years	8	12	2.08 (0.61, 7.18)	6	2.75 (0.73, 10.32)	--	-- ^c
20-40 years	14	29	1.65 (0.66, 4.14)	9	1.91 (0.67, 5.45)	5	2.08 (0.60, 7.21)
≥40 years	8	14	1.15 (0.35, 3.74)	7	1.74 (0.48, 6.35)	1	0.68 (0.09, 5.21)
<i>P</i> -trend			0.424		0.400		0.360
Quit drinking							
≥0-<5 years ago	7	9	1.95 (0.58, 6.58)	5	2.11 (0.54, 8.28)	2	2.41 (0.42, 13.83)
5-15 years ago	8	15	1.12 (0.35, 3.58)	4	1.76 (0.49, 6.35)	2	0.86 (0.15, 4.92)
≥15 years ago	15	32	1.58 (0.62, 4.00)	11	1.94 (0.70, 5.39)	2	1.81 (0.28, 5.07)
<i>P</i> -trend			0.220		0.156		0.477
Among current drinkers							
Drinking Intensity							
up to 1 drink per day	20	40	1.07 (0.49, 2.29)	9	0.77 (0.30, 2.01)	10	1.32 (0.42, 4.16)
1-2 drink per day	7	29	0.54 (0.20, 1.48)	6	0.61 (0.19, 1.94)	2	0.45 (0.09, 2.38)
>2 drink per day	11	33	0.83 (0.34, 2.02)	9	1.12 (0.42, 3.00)	2	0.69 (0.15, 3.18)
<i>P</i> -trend			0.918		0.716		0.778
Duration of drinking							
≥0-<40 years	10	28	0.82 (0.30, 2.24)	5	0.72 (0.21, 2.39)	5	1.08 (0.24, 4.78)
40-50 years	18	42	0.88 (0.40, 1.92)	10	0.76 (0.30, 1.97)	8	1.43 (0.47, 4.37)
≥50 years	12	35	1.05 (0.43, 2.53)	9	1.21 (0.43, 3.37)	2	0.71 (0.14, 3.63)
<i>P</i> -trend			0.834		0.826		0.900

a: 111 cases have been included in the final analysis;

b: the adjusted model contains main exposure, matching variables (race and age) and potential confounders (family history, physical activity and history of vasectomy);

c: There were no cases in this category.