ALCOHOL CONSUMPTION AND PROSTATE CANCER: A MINI REVIEW

Ch. Rizos¹, M. Papassava², Ch. Golias³, K. Charalabopoulos¹, *
¹Medical Health Center of Paramythia, General Hospital “G. Hatzicostas”, Makryianni Av., 45001 Ioannina, Greece
²Department of Pediatrics, Medical Faculty, University of Ioannina, University Campus, 45110 Ioannina, Greece
³Department of Physiology, Medical Faculty, Clinical Unit, University of Ioannina, University Campus, 45110 Ioannina, Greece

Prostate cancer has become a major public health problem worldwide although the etiology of prostate cancer remains largely unknown. Dietary factors, dietary supplements, and physical activity might be important in the prevention of the disease. In the majority of studies published, it was observed that high consumption of meat, alcohol and dairy products has been linked to a greater risk. Specifically, alcohol use, and particularly heavy use, may cause cancers of liver, esophagus, larynx, pharynx and oral cavity, with risks for the aero-digestive cancers. Moderate use among women has been related with increases in breast cancer. Alcohol consumption is a modifiable lifestyle factor that may affect prostate cancer risk. Alcohol alters the hormonal environment and in parallel, containing chemical substances such as flavonoids (red wine), may alter tumor cell growth. In this mini review, the relation between alcohol consumption and prostate cancer risk is analyzed.

Key Words: alcohol, prostate cancer, diet.

Alcohol consumption is generally measured in drinks per day, with a “typical” drink of alcohol containing about 15 g of ethanol irrespective of the type of beverage consumed (beer, wine and liquor, straight or mixed). Alcohol use, and particularly heavy use, may be causative of cancers of liver, esophagus, larynx, pharynx and the oral cavity, with risks for the aero-digestive cancers rising to about two — to — fourfold among heavy drinkers [1]. Alcohol consumption may also cause cancer at other sites. However, the evidence is less certain. Moderate use among women has been related with increases in breast cancer; summary analyses showed about a 10% increase in incidence of this disease with each alcoholic drink consumed daily [2, 3]. Increased risks for pancreatic cancer and colon tumors have also been related to alcohol use in some studies [4, 5].

In this presentation, the evidence that alcohol consumption is related to risk for prostate cancer is reviewed. Alcohol consumption, in studies of the association between alcohol and prostate cancer, has been reported quantitatively by drinks per day, qualitatively, by heavy or excess drinking, and by the diagnostic category of alcoholism. In this review we consider alcohol consumption of less than three drinks per day as moderate and consumption of seven or more drinks per day as abusive. Alcohol consumption is a modifiable lifestyle factor that may affect prostate cancer risk. Alcohol alters the hormonal milieu and in parallel, containing chemical substances such as flavonoids (red wine), may alter tumor cell growth [6].

EXAMINATION OF THE EPIDEMIOLOGICAL EVIDENCE FOR THE ALCOHOL AND PROSTATE CANCER ASSOCIATION

A population-based case-control study which was carried out in Montréal, accrued over 4000 men in total, including cases of prostate cancer, other cancers, and population controls. Beer was the most prevalent type of alcohol consumed in this population and showed the strongest association with prostate cancer. Risk of prostate cancer increased with increasing cumulative consumption of alcohol. There was no decrease in risk after quitting. The results were consistent with an increase in the risk of prostate cancer due to alcohol consumption [7]. Another study based on vital statistics in Japan reported a 2.5-fold increase in prostate cancer deaths among daily drinkers of strong liquor [8]. None of these studies provided quantitative information about the amount of alcohol use [9]. In a population-based case-control study from Seattle with 753 middle-aged newly diagnosed cancer patients, a potential reduced relative risk of prostate cancer associated with increasing level of red wine consumption was seen, and consumption of liquor or beer was not associated with prostate cancer [6]. Significantly increased risk for prostate cancer have been detected in a large cohort of alcohol abusers from Denmark and among alcoholics from Sweden who were less than 65 years of age but not among those 65 years or older [10,11]. The pooled standardized incidence ratio for alcohol abusers was 1.22 (95% confidence interval (CI) = 1.04, 1.42) for these two Scandinavian studies [12]. The Harvard Alumni Health Study, which prospectively followed 7612 Harvard alumni found a positive association between moderate alcohol consumption and the risk of prostate cancer [13]. The risk was especially related to liquor, but not wine or beer, consumption. Men who initiated drinking eleven years before the start of the study had a two-fold increased risk of prostate cancer. A population-based case-control study from Iowa showed...
a positive relationship between prostate cancer and alcohol consumption, and the risk was not limited to any specific kind of alcohol [14]. Men who consumed < 22 g of alcohol per week were at increased risk compared with non-drinkers. Data suggested that obesity was a risk factor for more clinically significant prostate cancer. Two small autopsy studies reported in the 1960s, found a lower prevalence of prostate cancer in patients with cirrhosis than in controls, suggesting that physiologic changes associated with cirrhosis may reduce prostate cancer risk. Controversially, in a hospital-based case-control study in Italy, with a total of 2663 of men younger than 75 years old, and 1551 controls showed no consistent association with prostate cancer risk, but a statistically inverse trend in risk for benign prostate hyperplasia. This may be due to hormonal correlates (i.e. lower androgen levels) of heavy alcohol drinkers [15]. Small latent cancers, which are over-represented in autopsies, were not distinguished from more aggressive neoplasms in these studies. Another population-based case-control study in Sweden, including 1499 cases and 1130 controls, showed no association between recent alcohol consumption and advanced, sporadic or familial prostate cancer, with the exception of borderline positive association with localized disease. Prostate cancer cases were more likely in current or former drinkers than in controls but there was no association between recent total alcohol, beer, wine and liquor consumption and risk of overall prostate cancer [16]. A pooled retrospective setting in Denmark with a study population of 12,989 subjects drawn from three different cohorts showed that neither amount nor type of alcohol is associated with the risk of prostate cancer [17]. A large cohort study in Baltimore (47,843 men) showed that moderate or greater alcohol consumption was not a strong contributor to prostate cancer risk. Cancer risk was greatest among men who consumed an average of 150 g of alcohol per week or more, but who drank only 1–2 days per week. So, the infrequent consumption of large amounts of alcohol is possibly a strong contributor to prostate cancer risk [18].

Most of the quantitative studies on alcohol use and prostate cancer have considered risks only up to levels of consumption of about three drinks or more per day. Increased prostate cancer risk was found in an Iowa cohort as less than one drink per day and a non significant increase in risk was found in the National Health and Nutrition Examination Survey Epidemiology Follow-up Study cohort I at more than three drinks per day [19, 20].

Other cohort studies showed no association in the range of alcohol use up to about three drinks per day [20–23, 18]. No prostate cancer excesses were noted at moderate levels of alcohol use in population-based case-control studies that reported detailed information on alcohol consumption except for a modest non significant excess noted in a Swedish study at one or more drinks per day [13, 24–27]. Few studies have examined a quantitative relation between heavy alcohol use and prostate cancer. In a US population-based case-control study, consumers of eight or more drinks per day had a significantly increased risk of this disease (relative risk = 1.9; 95% CI: 1.3, 2.7) [24]. Risks were similarly elevated among blacks and whites and among recent and former drinkers and similar risks were seen for beer and liquor independently, but not seen for wine.

A US cohort study of participants in a prepaid health plan showed no excesses after an average follow-up of 4.6 years; however, only five cases of prostate cancer occurred in the high-consumption group [15]. A non significant excess risk was noted among heavy drinkers in one hospital-based case-control study, but no excess was seen in three other hospital-based studies [28–31]. A higher prostate cancer risk was seen in men who consumed large amounts of alcohol infrequently in a large cohort study in Baltimore [18]. Interestingly, a meta-analysis of epidemiology studies published from 1976 to 1997, including six cohort and 27 case-control studies, found an overall relative risk estimate of 1.05 (95% CI: 0.98, 1.11) for prostate cancer among men who reported any alcohol consumption [12]. However, categorizing individuals as never ever consuming alcohol was done in different time frames with varying definitions. This may lump light drinkers and former drinkers with nondrinkers for some study definitions. To avoid such misclassification, levels of consumption were pooled. Based on a linear dose-response model, a pooled analysis showed an odds ratio of 1.21 (95% CI: 1.05, 1.39) for prostate cancer among men who drank four drinks per day, suggesting that daily consumption of four alcoholic drinks per day is associated with about a 21% increased risk for prostate cancer among heavy drinkers, or that 17.4% of prostate cancer among men who drink heavily is attributable to alcohol. However, the linear estimate included data from studies without alcohol consumption levels as high as four drinks per day which required linear extrapolation [12].

**HORMONAL AND MOLECULAR PARTICIPATION**

Both acute and chronic alcohol consumption tend to result in greater serum estrogen and lower androgen levels in both men and women [32]. Breast cancer in women is widely considered to be a disease of estrogen excess, consistent with excesses of this disease found in women who consume alcohol [32, 33]. Evidence suggests that the effect of alcohol is modulated by polymorphisms in genes encoding enzymes for ethanol metabolism (e.g., alcohol dehydrogenases), folate metabolism and DNA repair [32]. Plausible ways of alcohol carcinogenicity include genotoxicity of acetaldehyde (the main metabolite of ethanol), increased estrogen concentration (important for breast cancer and perhaps other hormone responsive tumors), a role as solvent for tobacco carcinogens, production of reactive oxygen species and nitrogen species as well as changes in folate metabolism [33]. Environment likely modifies the risk of both prostate and breast cancer, and this risk can vary > 10-fold. There is also species specificity, since there is no risk for prostate cancer in any other aging mammal except the dog. Prostate and breast cancer appeared at the same time 65 million years ago with the development of mammals [34].
The epidemiology of prostate cancer strongly suggests that environment factors, particularly diet and nutrition, are major determinants of risk for this disease, and evidence is mounting that there are important genetic risk factors for prostate cancer. The recent development of the Western-type diet is associated with breast and prostate cancer throughout the world. The exposure to and metabolism of estrogens and the dietary intake of phytosterogens, combined with fat intake, obesity, and burned food processing may all be related to hormonal carcinogenesis and oxidative DNA damage [35]. Estrogens, alone or in combination with androgens might influence aberrant growth and/or malignancy of the prostate gland. Estrogens elicit their effects via estrogen receptors in the prostate. Estrogen in combination with testosterone was shown to be effective in inducing prostate carcinogenesis in tissue recombinant models. In those models, the absence of the retinoblastoma tumor suppressor gene predisposed prostate epithelial cells to hormonal carcinogenesis [36].

As prostate cancer appears to be more closely linked to androgen excess, alcohol-related prostate carcinogenesis could operate through other pathways [37]. Human prostate carcinomas are often androgen sensitive and react to hormonal therapy by temporary remission, followed by relapse to an androgen-insensitive state. Steroid hormones, particularly androgens, play a major role in human prostate carcinogenesis but the precise mechanism is unknown. The possible involvement of estrogenic hormones is not entirely clear. A multifactorial general hypothesis of prostate carcinogenesis emerges with androgens acting as strong tumor promoters acting via androgen receptor–mediated mechanisms to enhance the carcinogenic activity of strong endogenous genotoxic carcinogens, such as reactive estrogen metabolites and estrogen-and prostatitis-generated reactive oxygen species and possible weak environmental factors such as diet, and polymorphic genes that encode for steroid hormone receptors and enzymes involved in the metabolism and action of steroid hormones [38]. Earlier studies observed positive association between insulin-like growth factor-I (IGF-I) and prostate cancer. Recent epidemiologic studies have reported suggestive evidence for a positive association between IGF-binding protein-3 (IGFBP-3) and prostate cancer risk; a result contraindicating the earlier assumption that high levels of IGFBP-3 would be protective against prostate cancer. In a prospective cohort of 17,049 men in Australia, high levels of IGFBP-3 (but not IGF-I) were associated with an increased risk of prostate cancer [39].

Alcohol may improve the permeability of cell membranes to carcinogen agents, alter carcinogen metabolizing enzyme activity, and inhibit DNA repair [40]. Evidence suggests that the effect of alcohol is modulated by polymorphisms in genes encoding enzymes for ethanol metabolism, folate metabolism and DNA repair. The exact mechanisms have not been defined fully, although plausible events include: a genotoxic effect of acetaldehyde, the main metabolite of ethanol; increased estrogen concentration; a role as solvent for tobacco carcinogens; production of reactive oxygen species and nitrogen species; and changes in folate metabolism [4]. Alcohol can alter first pass metabolism in the liver of carcinogens, such as the nitrosamines, and may impact on DNA methylation affecting gene regulation [41]. Additionally, alcohol consumption impacts energy balance and body mass, factors that could be of importance for disease such as breast and prostate cancer [42, 43].

The data about studies on the relation between alcohol consumption and prostate cancer risk are summarized in Table.

**METHODODOLOGICAL ISSUES**

If alcohol causes or modifies the development of prostate cancer, this may occur only at high levels of exposure. Of the few analytical studies with quantitative estimates of alcohol intake, effects of high levels of consumption were considered in only one cohort study [12]. However, this investigation was limited for assessment of high exposure risks reporting on only five cases in the high-exposure group. One population-based study [7] and four hospital-based case-control studies [8, 11, 13, 14] reported a relation between a heavy alcohol use and prostate cancer. Alcohol consumption in cases compared with hospital controls may not give valid comparisons, as alcohol use among hospital controls may differ from that of the general population. Heavy alcohol use is associated with a number of diseases and conditions requiring hospitalization, while moderate alcohol consumption may actually reduce the likelihood of hospitalization because this level of consumption may lead to reduce risks of various diseases including heart disease. Heavy alcohol users tend to be under-represented among study participants, and participants may tend to under-report alcohol use. If this occurred differentially for cases and controls, substantial bias could result.

The variation in reported risk of prostate cancer and alcohol consumption between studies may also be due to the varying methods of reporting alcohol consumption. In the various studies of prostate cancer, for example, measures of the timing of alcohol use included, more than six times per year [20], 24-hour recall [24], regular use for more than 6 months [18], use in the past year [18, 20], use in the past 3 years [21, 22], use in the 10 years prior to the reference date [17], and use during the “current” time when questionnaire data were being collected [16]. Three studies reported on the number of occasions when alcohol was consumed [44–46]. Two other studies did not clearly identify whether they were reporting volume of ethanol or volume of alcoholic beverages [31, 43]. A sixth study reported on men who never used alcohol, reformed drinkers, and those who consumed more than three drinks per day [46]. Among the remaining studies with quantitative dose data [5, 6, 11–13, 16–18], the average alcohol consumption rate per study ranged from 0.3 drinks per day to 5.3 drinks per day, suggesting a wide variation in consumption by heterogeneous population or potential errors in reporting [8].
CONCLUSION

Despite variability of methodological issues and different data reported up-to-date, one may conclude that moderate alcohol consumption up to about three drinks per day does not appear to influence prostate cancer risk; however, heavy consumption of about seven or more drinks per day may be associated with an excess risk for this disease, as indicated by some studies among alcoholics and other heavy users of alcohol. The level of risk at this level of exposure is modest, however, and could be due to confounding by other causal factors or due to biases inherent in observational studies. As alcohol use patterns can vary with age, time-dependent evaluations of alcohol use and prostate cancer risk are needed. Cohort studies with quantitative assessment among heavy alcohol users are needed to address the limitations of retrospective studies. Also, the findings from early autopsy studies, suggest that liver cirrhosis is negatively associated with prostate cancer need to be re-evaluated employing modern pathologic concepts to focus research on prostate tumors of potential clinical significance [45, 46].

REFERENCES

Table. Main studies on relation between alcohol consumption and prostate cancer risk

<table>
<thead>
<tr>
<th>Study type/country/year</th>
<th>Number of participants</th>
<th>Alcohol consumption estimates</th>
<th>Relationship between alcohol consumption and prostate cancer risk</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy/2004</td>
<td>2663 (1294 PC + 1369 BPH cases)</td>
<td>Wide range from &lt; 3 dr/d to &gt; 7 dr/d</td>
<td>Alcohol &amp; PC no association, inverse relationship with BPH. OR: 0.88 for</td>
<td>[15]</td>
</tr>
<tr>
<td>U.S.A/1996</td>
<td>981 men (479 blacks and 502 whites)</td>
<td>&gt; 8 dr/d</td>
<td>&lt; 3 dr/d, 0.71 for 3–4 dr/d, 0.79 for 5–6 dr/d, 0.65 for &gt; 7 dr/d</td>
<td>[24]</td>
</tr>
<tr>
<td>USA/1998, 2006</td>
<td>699 white prostate cancer cases, review</td>
<td>Alcohol intake comparing ever, current, and former, even the highest reported level of alcohol consumption</td>
<td>No risk found for prostatic carcinoma</td>
<td>[29–30]</td>
</tr>
<tr>
<td>Italy/1994</td>
<td>281 cases</td>
<td></td>
<td>RR = 1.2 and 0.9 for &lt; 5 and or = 5 dr/d, respectively, compared with wine abstainers, beer (RR = 1.1 for beer drinkers compared with beer abstainers), and spirit (RR = 0.8 for spirit intake compared with beer abstainers)</td>
<td>[31]</td>
</tr>
<tr>
<td>Denmark/1994</td>
<td>15,214 men</td>
<td>Alcohol abusers (RR = 1.4; 95% CI 1.2–1.8)</td>
<td>Cohort studies</td>
<td>[10]</td>
</tr>
<tr>
<td>Sweden/1992</td>
<td>8340 men</td>
<td>Diagnosis of alcoholism (SIR = 1.0, CI = 0.8–1.4)</td>
<td>For 15 studies; RR of 1.05 (95% CI, 0.91–1.20) for each additional drink of alcohol per day or a RR of 1.21 for 4 dr/d for all 33 studies, a RR of 1.02 was found for each additional drink of alcohol per day no association between prostate cancer and alcohol consumption</td>
<td>[11]</td>
</tr>
<tr>
<td>Denmark/Sweden and 27 case-control studies</td>
<td></td>
<td></td>
<td>Multivariate relative risks (95% CI) for 1 drink/month to &lt; 3 drinks/week, 3 drinks/week to &lt; 1 dr/d, 1 to &lt; 3 dr/d, and &gt; 3 dr/d were 1.33 (0.88–2.01), 1.65 (1.12–2.44), 1.85 (1.29–2.64), and 1.33 (0.86–2.05), respectively</td>
<td>[12]</td>
</tr>
<tr>
<td>Harvard Alumni Health Study</td>
<td>7612 men</td>
<td>123.1 g/week, of which 28.6% was from wine, 15.8% from beer, and 55.6% from liquor (&lt; 105 g/week v2 &gt; 105 g/week)</td>
<td>Compared with nondrinking, the hazard ratio for consumption increased slightly from an average of 5.0–14.9 g/day (hazard ratio (HR) = 1.05, 95% CI 0.94, 1.18) to 30.0–49.9 g/day (HR = 1.13, 95% CI 0.96, 1.33), but it was not increased at &gt; 50 g/day (HR = 1.00, 95% CI 0.77, 1.31). Compared with abstainers, risk was greatest among men who consumed an average of &gt; 105 g/week but who drank on only 1–2 days per week (HR = 1.64, 95% CI 1.13, 2.38)</td>
<td>[13]</td>
</tr>
<tr>
<td>Baltimore/2004</td>
<td>47,843 men</td>
<td></td>
<td>Compared with wine, alcohol, and dietary factors (RR = 1.7; 95% CI = 1.0–2.7). Risk was confined to older (age 70+ years) farmers (RR = 2.2; 95% CI = 1.1–4.3); no effect among younger farmers (RR = 1.0; 95% CI = 0.4–2.1)</td>
<td>[18]</td>
</tr>
<tr>
<td>Iowa/1999</td>
<td>1177 cancer free men</td>
<td></td>
<td>Increased risk of prostate cancer after adjustment for age, smoking, alcohol, and dietary factors (RR = 1.7; 95% CI = 1.0–2.7). Risk was confined to older (age 70+ years) farmers (RR = 2.2; 95% CI = 1.1–4.3); no effect among younger farmers (RR = 1.0; 95% CI = 0.4–2.1)</td>
<td>[19]</td>
</tr>
<tr>
<td>Netherlands/1999</td>
<td>58,279 men, aged 55–69 years</td>
<td>Consumption of alcoholic beverages</td>
<td>RRs (95% CI) in the intake category of &gt; 15 g/day were 3.3 (1.2–9.2) and 2.3 (1.2–4.7), respectively</td>
<td>[22]</td>
</tr>
<tr>
<td>Canada/1999</td>
<td>1623 histologically confirmed prostate cancer cases</td>
<td>OR = 3.1, 95% CI = 1.8–5.4</td>
<td></td>
<td>[25]</td>
</tr>
<tr>
<td>Population studies</td>
<td>Over 4000</td>
<td>Alcohol abusers</td>
<td>High risk for those started &lt; 15 years old (odds ratio = 3.8; 95% CI: 1.6–9.3)</td>
<td>[7]</td>
</tr>
<tr>
<td>Japan/1992</td>
<td>753 middle aged men</td>
<td>Alcohol consumers</td>
<td>Elevated risk from alcohol consumption for cancer of the prostate</td>
<td>[8]</td>
</tr>
<tr>
<td>Seattle/USA/2005</td>
<td>753 middle aged men</td>
<td>Alcohol consumers</td>
<td>Reduced risk of prostate cancer in red wine consumers, no relation of prostate cancer and alcohol or liquor</td>
<td>[6]</td>
</tr>
<tr>
<td>Iowa/USA/2000</td>
<td></td>
<td></td>
<td>&lt; 22 g alcohol per week (relative risk [RR] = 1.1; 95% CI = 0.6–2.1), 22–96 g alcohol per week (RR = 2.6; 95% CI 1.4–4.6) and &gt; 96 g alcohol per week (RR = 3.1; 95% CI 1.5–6.3) were at increased risk of prostate cancer. RR's were similar when assessing type of alcohol consumed (beer, wine or liquor)</td>
<td>[14]</td>
</tr>
<tr>
<td>Sweden/2005</td>
<td>1499 cases</td>
<td>Alcohol consumers</td>
<td>OR for risk of overall disease among men who drank more than 135 g of total alcohol per week versus non-drinkers was 1.2 (95% CI: 0.9, 1.5), p(trend) = 0.12</td>
<td>[16]</td>
</tr>
<tr>
<td>Denmark/2002</td>
<td>12,989 cases</td>
<td>Alcohol consumers</td>
<td>Drinkers of more than 13 beers, 13 glasses of wine, and 13 drinks of spirits had a risk of 1.03 (CI: 0.67, 1.60), 0.92 (CI: 0.42, 1.99), and 1.01 (CI: 0.52, 1.98), respectively, compared with abstainers</td>
<td>[17]</td>
</tr>
</tbody>
</table>

Notes: BPH – benign prostate hypertrophy; OR – odds ratio; PC – prostate cancer; dr/d – drinks per day; RR – relative risk; SIR – standardized incidence ratio; HR – hazard ratio.


Copyright © Experimental Oncology, 2010