

Alcohol consumption and risk of urothelial cell bladder cancer in the European Prospective Investigation into Cancer and Nutrition cohort

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Abstract

Findings on the association between alcohol consumption and bladder cancer are inconsistent. We investigated that association in the European Prospective Investigation into Cancer and Nutrition cohort. We included 476,160 individuals mostly aged 35-70 years, enrolled in ten countries and followed for 13.9 years on average. Hazard ratios (HR) for developing urothelial cell carcinoma (UCC; 1,802 incident cases) were calculated using Cox proportional hazards models. Alcohol consumption at baseline and over the life course was analyzed, as well as different types of beverages (beer, wine, spirits). Baseline alcohol intake was associated with a statistically non-significant increased risk of UCC (HR 1.03; 95% confidence interval (CI) 1.00-1.06 for each additional 12 grams/day). HR in smokers was 1.04 (95% CI 1.01-1.07). Men reporting high baseline intakes of alcohol (>96 grams/day) had an increased risk of UCC (HR 1.57; 95% CI 1.03-2.40) compared to those reporting moderate intakes (<6 grams/day), but no dose-response relationship emerged. In men, an increased risk of aggressive forms of UCC was observed even at lower doses (>6 to 24 grams/day). Average lifelong alcohol intake was not associated with the risk of UCC, however intakes of spirits > 24 grams/day were associated with an increased risk of UCC in men (1.38; 95% CI 1.01-1.91) and smokers (1.39; 95% CI 1.01-1.92), compared to moderate intakes. We found no association between alcohol and UCC in women and never smokers. In conclusion, we observed some associations between alcohol and UCC in men and in smokers, possibly due to residual confounding by tobacco smoking.

Novelty and Impact

Findings from the EPIC cohort do not suggest a clear detrimental effect of alcohol on bladder cancer risk. However, we found some association between alcohol and risk of the most aggressive forms of bladder cancer in men and in smokers. Among the different beverages, high intakes of spirits were associated with an increased risk of bladder cancer in men and in smokers, while beer and wine were not. Further studies confirming these results are warranted.

Introduction

An estimated 429,000 bladder cancer cases occurred worldwide in 2012, making it the ninth most common cause of cancer for both sexes combined. The disease is more common in more developed than less developed regions and in men than women (sex ratio of 3.5:1) [1]. In addition to gender, established risk factors include race [2], cigarette smoking [3], occupational exposure to aromatic amines and polycyclic aromatic hydrocarbons [4], arsenic in drinking water [5] and *Schistosoma haematobium* infection [6]. Whether alcohol consumption is a risk factor for bladder cancer remains controversial. A review of six cohort studies and 21 case-control studies published by the International Agency for Research on Cancer (IARC) showed that the evidence for an association between alcohol and bladder cancer is inconclusive [7]. A meta-analysis published in 2012, combining the evidence from 3 cohort and 16 case-control studies, showed no association between alcohol consumption and bladder cancer risk [8]. A second meta-analysis published in 2015, based on the same 19 studies, examined the dose-response relation between bladder cancer risk and alcohol drinking [9], and showed no evidence of such a relation. However, results from the included studies differed, and consequently a significant heterogeneity among the pooled estimates was reported in both meta-analyses.

We investigated the association between alcohol consumption and the risk of urothelial cell carcinoma (UCC), the main morphological type of urinary bladder cancer, in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. With 476,160 individuals and 1,802 incident UCC cases, this large cohort study aims at providing novel insights into the relation between alcohol consumption and UCC risk. Alcohol consumption at baseline and over the life course is analyzed, as well as different types of

alcoholic beverages (i.e. beer, wine, spirits). Also, we distinguish non-aggressive from aggressive UCCs. All analyses are presented by gender and smoking status.

Materials and Methods

Study participants

Design and methods of the EPIC cohort, including detailed description of the questionnaires used to collect data on lifestyle, health and sociodemographic characteristics, have been described previously [10,11]. Briefly, the cohort includes 23 centers in ten countries: Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden and United Kingdom. Participants were mostly 30–75 years at baseline (1991–2000), and were mostly recruited from the general population. 521,457 participants were included, and gave written, informed consent to the use of their data for research purposes. Information on socio-demographic characteristics, anthropometric measures, physical activity, medical history and alcohol and tobacco consumption was assessed at recruitment using validated country-specific or center-specific lifestyle questionnaires designed to capture habitual consumption over the preceding year. Energy (kcal/day) was estimated using the EPIC Nutrient Database [12]. Height and weight were measured in most of the centres, except for Oxford (UK), France and Norway where they were self-reported. Body mass index (BMI) was calculated as weight in kilograms divided by squared height in metres (kg/m^2).

From the whole EPIC cohort of 521,324 subjects, we excluded 25,184 subjects with prevalent cancer (any cancer except nonmelanoma skin cancer), 4,148 without follow-up data and 15,832 subjects without information on alcohol consumption. A total of 476,160 subjects were included in the present study.

Cancer ascertainment was mostly based on population cancer registries, except for France, Germany, Italy (Naples center) and Greece, where a combination of methods including health insurance records, cancer and pathology hospital registries, and active follow-up were used. Mortality data were collected from registries at the regional or national

level. Subjects were followed up from study entry and until cancer diagnosis (except non-melanoma skin cancer), death, emigration or until the end of the follow-up period, whichever occurred first. Overall, 1,237 (0.26%) were lost to follow-up. The date of the last complete follow-up ranged from June 2008 to December 2013, depending on the center.

Exposure assessment

Participants reported on how many standard glasses of beer, wine, sweet liquor, distilled spirits, and fortified wine they had consumed per day or per week during the 12 months prior to recruitment. Lifetime alcohol consumption was assessed based on self-reported weekly consumption of those alcoholic beverages at ages 20, 30, 40, and 50 years in the lifestyle questionnaire. The average lifetime daily consumption was calculated and used in the analyses. The duration of alcohol consumption was calculated by the difference between the age when an individual started to drink alcohol and the age of last reported consumption (the latter was the same as the age at recruitment for current drinkers). Information on lifetime alcohol consumption was available for 76% of the individuals with baseline alcohol consumption. For the present analysis, liquor, spirits, and fortified wine were combined in a single category (i.e. 'spirits') because of their common high concentration of alcohol per volume of drink. We used alcohol from alcoholic beverages as exposure, both as a continuous and a categorical variable. When used as continuous, the unit of increment was one standard drink a day, corresponding to 12 grams of alcohol a day (g/d). When used in categories, a gender-specific reference group was implemented: >0–6 g/d for males (M) and >0–3 g/d for females (F). The remaining categories were: non-drinker, >6–12(M)/>3–12(F) g/d, >12–24 g/d, >24–60 g/d, >60–96(M)/>60(F) g/d and >96(M) g/d.

Endpoint

The primary endpoint was the first occurrence of primary UCC (topography code 67 and morphology codes 812-813 according to the ICD-Oncology, third edition). Other bladder cancer types and cases with behaviors coded as ‘benign’ and ‘uncertain whether benign or malignant’ were censored at time of diagnosis, while cases with behaviors coded as ‘carcinomas in situ’ or ‘malignant’ were included as cases. UCCs were further classified as non-aggressive (pTa, Grade 1 and 2) and aggressive (pT1 and higher or CIS or Grade 3, including pTa, Grade 3). In a sensitivity analysis, we also tested an alternative stratification in less advanced (pTa/CIS/pT1) and more advanced UCCs (pT2 and higher).

Statistical methods

Multivariable Cox proportional hazards regression models were used to assess the impact of alcohol intake on UCC risk. Hazard ratios (HRs) and confidence intervals (CIs) were estimated using age as the underlying time scale, with entry time defined as the participant’s age at baseline and exit time as age at UCC diagnosis or censoring (diagnosis of any cancer, except nonmelanoma skin cancer; death; emigration; loss to follow-up; or end of follow-up, whichever came first). All models were stratified by age at recruitment (1-year intervals), gender and study center and adjusted for smoking status (current, 1-15 cigarettes/day; current, 16-25 cigarettes/day; current, 26+ cig/day; current, pipe/cigar/occasional cigarettes smoker; current/former, missing; former, quit 11-20 years; former, quit 20+ years; former, quit ≤ 10 years; never; missing), energy intake (kcal/day; continuous), BMI (continuous), physical activity (active; moderately active; moderately inactive; inactive; missing) and educational level completed (primary school; secondary

school; university degree or higher; technical/professional school; none; missing). Adjustment for smoking status was kept in the models even when we limited the analysis to smokers only (current and former).

The following sub-analyses were conducted: association between alcohol and UCC risk by sex, smoking status (never; ever (former and current)) and by age (5-year intervals). In a sensitivity analysis we excluded UCC cases diagnosed within the first 2 years of follow-up to control for potential changes in alcohol consumption due to early symptoms of UCC. In a second sensitivity analysis, we limited the analysis to the study-centers in which information on occupational exposure was available, and we additionally adjusted the alcohol estimates for occupational exposure to aromatic amines (e.g. workers in dye production, textile and leather dying, and hairdressers) and polycyclic aromatic hydrocarbons (e.g. workers in the transport and asphalt sector, car repair stations, and refineries) [4].

All statistical tests were two-sided, and P-values < 0.05 were considered statistically significant. All analyses were conducted using SAS software, version 9.4 (SAS Institute, Cary, NC).

Results

A total of 476,160 participants (70.1% females) were followed for a mean of 13.9 years, during which 1,802 UCC cases (1,273 male, 529 female) were diagnosed: 871 aggressive, 384 non-aggressive and 547 unclassified cases (Table 1). Mean age at recruitment was 51.2 years. Baseline characteristics according to different levels of alcohol consumption are shown in Table 2. The educational level attained and the proportion of smokers, the proportion of moderately active and active, as well as energy intake, steadily increased with increasing levels of alcohol consumption in both sexes.

In Table 3 we reported the estimates of the association between alcohol consumption, analyzed as a continuous variable, and the risk of UCC. The HR for baseline alcohol intake was 1.03 (95% CI 1.00-1.06) for each additional 12 g/d. The risk estimates in ever and never smokers were 1.04 (95% CI 1.01-1.07) and 0.93 (0.84-1.03), respectively. We stratified the population by age at baseline using the following categories: <50 years (UCC cases/number at risk: 272/201,914), 50-54 (334/104,515), 55-59 (447/76,863), 60-64 (499/61,000) and ≥ 65 (250/31,868) and the corresponding UCC risk estimates for each additional 12 g/d were 0.99 (95% 0.92-1.06), 1.06 (1.00-1.13), 1.05 (1.00-1.11), 1.01 (0.95-1.07), 0.98 (0.88-1.10). Average lifetime consumption was not statistically significantly associated with bladder cancer. In addition, no significant association was observed between baseline and lifetime consumption of beer, wine and spirits and risk of UCC.

In Table 4 we reported the estimates of the association between alcohol consumption, analyzed as a categorical variable, and the risk of UCC. No clear dose-response relationship between baseline alcohol intake and UCC risk emerged. However, men who reported high intakes of alcohol (>96 g/d) had an increased risk of UCC (HR 1.57; 95% CI 1.03-2.40) compared to those who reported moderate intakes ($>0-6$ g/d). A similar pattern was observed

in smokers. Notably, all 26 UCC cases in the high intake category were male smokers. There was no significant association between average lifetime consumption and bladder cancer.

No significant association was observed between baseline consumption of beer, wine and spirits and risk of UCC (Supplementary Table 1). However average lifetime intakes of spirits > 24 g/d were associated with an increased risk of UCC in men (1.38; 95% CI 1.01-1.91) and smokers (1.39; 95% CI 1.01-1.92), as compared to moderate intakes (Supplementary Table 2).

Baseline and average lifetime alcohol intakes, analyzed as continuous variables, were not associated with an increased risk of aggressive UCC (Supplementary Table 3). No clear dose-response relationship emerged when alcohol consumption was analyzed as a categorical variable (Supplementary Table 4). Men who reported a baseline consumption of more than 6 to 24 g/d and >96 g/d had a significantly increased risk of aggressive UCC compared to men who reported moderate intakes (>0-6 g/d). However, men who reported more than 24 to 96 g/d had no significant increased risk of aggressive UCC. A similar non-monotonous trend was observed in smokers. No significant association between alcohol consumption and risk of non-aggressive UCC was observed (data not shown). No significant association between alcohol consumption and risk of non-aggressive UCC was observed. When we used the classification based on tumor growth only, we found no association of alcohol consumption with either less advanced UCCs (pTa/CIS/pT1; n=911) or more advanced UCCs (pT2 and higher; n=287) (data not shown). We found no significant association between the duration of alcohol consumption and the risk of UCC (data not shown).

In Supplementary Table 5 we reported a complete multivariable model to show the association of gender, education, smoking status, physical activity, BMI and energy intake

with the risk of UCC. Gender and smoking status were significantly associated with the risk of UCC.

When we excluded the 124 UCC cases diagnosed within the first 2 years of observation, results remained essentially unchanged. Moreover, no significant variation was observed when we limited the analysis to the study-centers in which information on occupational exposure was available and we further adjusted for occupational exposure to aromatic amines and polycyclic aromatic hydrocarbons (data not shown).

Discussion

The results from this large cohort study across ten Western European countries do not suggest a clear association between alcohol consumption and the risk of UCC. Some evidence of a possible positive association between high intakes of alcohol and the risk of UCC was restricted to men and smokers. Also, a possible association between alcohol and the risk of aggressive UCC was also found in men and in smokers. However, no clear dose-response relationship between alcohol intake and UCC risk and no significant association in never smokers emerged.

The mechanisms by which alcohol consumption may exert its carcinogenic effect are not fully understood. Acetaldehyde, the first metabolite of ethanol, accounts for a considerable part, if not most, of the carcinogenicity of alcohol drinking [7,13]. Acetaldehyde is excreted through the urinary tract and is present in the urine after drinking of alcohol [14,15], and therefore a mechanistic role of alcohol consumption in the occurrence of UCC is plausible. Such a causal relationship is also supported by that polymorphisms in genes encoding the alcohol-metabolizing enzymes aldehyde dehydrogenase 2 and alcohol dehydrogenase 1B affect bladder cancer risk in a recent small case-control study [16]. On the other hand, alcoholic beverages might protect against UCC, as increased fluid intake dilute the carcinogens in the urine and increase the frequency of voiding, reducing contact of carcinogens with the bladder epithelium [17]. A large amount of epidemiological data on the association between alcohol and bladder cancer is available. In a monograph dedicated to personal habits and cancer risk, IARC reported a review of six cohort studies and 21 case-control studies on alcohol drinking and UCC risk, and concluded that the evidence for an association is inconclusive [7]. Two meta-analyses, published in 2012 and 2015, combining the evidence from 3 cohort and 16 case-control studies, showed no overall association and no dose-response trend between alcohol consumption and bladder cancer risk [8,9]. The World

Research Fund International Continuous Update Project classified the evidence of the association between alcohol and bladder cancer as limited and inconclusive [18].

In agreement with the existing literature, the results of our study do not suggest a clear association between alcohol consumption and bladder cancer risk. We found that the average intake of alcohol over the life course was not associated with an increased risk of UCC. Baseline alcohol intake analyzed as a continuous variable was associated with a significant increased risk of UCC only in smokers (4% increase for each additional drink), and high baseline intakes of alcohol (>96 g/d) increased the risk of UCC only in men and in smokers. The presence of an association in smokers might suggest a synergistic or exacerbating effect of acetaldehyde (or derived products) in conjunction with soluble tobacco carcinogens in contact with the bladder epithelium. We found no clear dose-response relation between alcohol and UCC risk, and no evidence of an association in women and in never smokers. Altogether, these results suggest that if an increased risk of UCC exists, it is probably weak and mainly confined to the higher consumption categories. However, some new evidence of an association between alcohol consumption and the risk of the most aggressive forms of UCC was found in men and in smokers. These results might suggest a possible role of alcohol in facilitating tumor progression, or suggest that alcohol selectively increases the risk of fast growing forms of UCC. To our knowledge, no other papers reported on the association between alcohol and subtypes of UCC, therefore further studies are needed to clarify this issue.

The role of residual confounding by smoking cannot be ruled out in our study. Tobacco smoking is the leading cause of UCC, with a population attributable risk of 50% in both sexes [19], and it is positively correlated with alcohol drinking. Therefore smoking can act as a powerful confounder in the link between alcohol and UCC. In the meta-analysis by Pelucchi et al. [8] the excess risk of bladder cancer due to high consumption of alcohol

vanished when the smoking-unadjusted estimates were removed from the analysis. Similarly, in our study, the smoking-adjusted and smoking-unadjusted UCC risk estimates were 1.07 (95% CI 1.04-1.10) and 1.03 (95% CI 1.00-1.06), respectively, for each additional drink per day reported at baseline.

With regard to the different types of alcoholic beverages, we found that an average lifetime consumption of more than 2 glasses of spirits a day increased the risk of UCC in men and in smokers, while no significant association with beer and wine was found. The higher concentration of alcohol per drink volume in spirits compared to beer and wine might explain these results. However, residual confounding by smoking might again be accountable for the observation, as no dose-response relationship between spirits and UCC risk was observed and no association was observed in never smokers. In contrast to our findings, a 2010 meta-analysis reported a negative association of beer and wine with bladder cancer and no association of spirits [20]. The authors hypothesized that certain phenolic compounds, namely Xanthohumol in beer and Resveratrol in wine, might be responsible for the possible protective effect [21,22]. However, the meta-analysis was based on a small number of investigations and significant heterogeneity was reported between studies reporting on beer and wine consumption. Also, none of the studies included in the meta-analysis showed a significant association in non-smokers.

The strengths of this study include its prospective design, long follow-up and multi-center European design. We could analyze alcohol consumption at baseline and over the life course, as well as different types of alcoholic beverages. In addition, we were able to select UCC tumors only, to limit possible differential effects of alcohol on other rare bladder cancer types. The main novelty our paper is given by the possibility to analyze a subset of UCC tumors according to their stage. Since tobacco smoking is the most important bladder cancer risk factor we carefully adjusted for its potentially confounding effect by including smoking

status, intensity and time since quitting in all statistical models, and by presenting results stratified by smoking status. However, residual confounding by tobacco smoking could still be present. This is an important limitation, together with the potential measurement errors from dietary questionnaires, which potentially led to recall, response and misclassification bias for the alcohol exposure assessment. Also, information on race was missing; however participants were mostly Caucasians. Another limitation is given by the lack of information on the changes in the covariates, especially smoking, during the long follow-up of the study. In addition, despite the large cohort size, we found a relatively small number of UCC cases in certain subgroups of subjects (e.g. non-smokers) therefore the power for testing the association between alcohol and UCC risk in those subgroups was limited.

In conclusion, our findings do not suggest a clear detrimental effect of alcohol consumption on bladder cancer risk. Residual confounding by smoking might explain the association between high intakes of alcohol and the increase in UCC risk observed in men and in smokers. However, new studies investigating the association between alcohol consumption and the most aggressive forms of UCC are warranted.

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Conflicts of interest: The authors have declared no conflicts of interest.

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