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Elevated risk of cancer of the urinary tract for alcohol drinkers: a meta-analysis

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Key words: alcohol drinking, alcoholic beverages, bladder neoplasms, meta-analysis, urologic neoplasms.

Abstract

Objectives: Recent narrative reviews have concluded that there is no support for an association between alcohol consumption and urinary tract cancer. Many individual studies, however, have reported positive associations, although rarely statistically significant. The purpose of this meta-analysis is to summarize and quantify this relationship with more statistical power and to perform a sensitivity analysis on the study characteristics.
Methods: We included 16 epidemiological studies published up to April 1999 and calculated summary odds ratios (SORs), both upgraded and adjusted for age, sex and smoking by meta-regression analyses. The age- and smoking-adjusted SORs (current alcohol drinking vs. non-drinking) were 1.3 (95% CI 0.9–2.0) for six studies with men and 1.0 (95% CI 0.4–2.6) for four studies with women.
Results: The age-, sex- and smoking-adjusted SOR was 1.2 (95% CI 0.9–1.7) for seven studies with men and women combined.
Conclusion: Even though studies differed in methodology, the results were rather consistent. Subgroup analyses by type or amount of alcohol were not possible due to sparse data. We conclude that the available data suggest a slightly increased risk of urinary tract cancer from alcohol consumption for men. The risk related to alcohol consumption for women and the influence of the amount and type of alcohol remain unclear.

Introduction

Over the past four decades many epidemiological studies have been conducted to investigate determinants of cancer of the urinary tract [1–6]. These studies suggested that cancer of the urinary tract is influenced by environmental factors, such as cigarette smoking and occupational exposure to aromatic amines, and by chronic infections with *Schistosoma haematobium*. The impact of alcohol consumption on the risk of cancer of the urinary tract is less clear. Although some epidemiological studies have reported an elevated risk of cancer of the urinary tract for alcohol drinkers compared to non-drinkers, recent narrative reviews have concluded that there is no support for such an association [1–3, 6, 7]. The results of follow-up and case–control studies which have examined this association were rarely statistically significant. However, these non-significant results might also be explained by lack of statistical power in the individual studies. The purpose of the present study is to review the epidemiological literature systematically, by means of a meta-analysis with more statistical power, and to provide quantitative summary estimates of the risk of cancer of the urinary tract with emphasis on current alcohol use *vs.* non-use.

Materials and methods

Search strategy

Epidemiological studies were identified through a computerized Medline and Cancerlit search on follow-up and case–control studies published up to April 1999 using Medical Subjects Headings and free text words. The keywords used were urolo*, bladder, cyst*, vesic*, kidney, glomerul*, nephr*, pyel*, renal, ureteral, urethral, transitional cell, cancer, carcino*, tumo*, neo-

plasm*, onco*, risk, etiology, epidemiology, and caus*. References in relevant publications were examined further. For inclusion in this analysis, the articles had to provide sufficient information to estimate a summary odds ratio of newly diagnosed primary cancer of the urinary tract for current alcohol consumers compared to non-drinkers, *i.e.* exposure frequency distribution, exposure specific odds ratios or exposure-specific incidence rate ratios. Alcohol consumption is defined as current consumption of beer, wine or spirits at baseline (follow-up studies) or in the reference period (case–control studies).

Data collection

For each study, information was collected on study design (follow-up or case–control study), measuring instrument (interview or questionnaire) and anatomical site of the neoplasm (total urinary tract, bladder, renal pelvis or ureter). For case–control studies, additional information was gathered on the sources of the cases and controls (population-based or hospital-based). Case–control studies which used controls obtained from the general population or from hospitals were defined as population-based or hospital-based case–control studies, respectively. The study characteristics were used to evaluate sources of variation in effect sizes. We extracted data allowing us to calculate both unadjusted and adjusted odds ratios to estimate the relationship between current alcohol consumption and the risk of cancer of the urinary tract. We constructed 2×2 tables for each study, based on exposure frequency distributions, in order to calculate the unadjusted odds ratios. The method of Woolf [8] was used to estimate the variance of the unadjusted odds ratios. Adjusted odds ratios were extracted directly from the original reports. Because we considered age, sex and smoking to be the most important confounding variables, the authors of the original articles had to have adjusted for at least these three variables. If studies reported sex-stratified age- and smoking-adjusted odds ratios, we combined these estimates by calculating an age-, smoking- and sex-adjusted weighted average of the stratum-specific odds ratios. The inverse of the standard error was used as weight. For studies that reported separate adjusted odds ratios for several consumption strata, we estimated a total odds ratio for ''any use'' using the exposure-specific prevalence of the non-cases as weight [9].

Statistical analysis

To detect publication bias, we explored heterogeneity in funnel plots, plots of effect estimates against their estimated precision [10]. The funnel plot is based on the fact that the precision of effect estimates increases with sample size. Results from small studies will scatter on the left side of graph, with the spread narrowing among larger studies on the right side of the graph. In the absence of bias, the plot will resemble a symmetrical inverted funnel [11]. We examined funnel plot asymmetry visually and measured the degree of asymmetry using Egger's unweighted regression asymmetry test [11]. If a study had appeared in more than one publication, data from the last publication were used for statistical analysis. We estimated the summary odds ratios with random effects meta regression analysis using the STATA statistical software package [12]. The between-study variance was estimated iteratively, using the empirical Bayes method [13]. The summary odds ratios were only calculated for total current alcohol consumption. Subgroup analyses by type or amount of alcohol were not possible due to sparse data. The calculation of summary estimates for men or women combined or separately was based on different study sets. Therefore, we analyzed the results for men and women both separately and combined, depending on available data in the original studies. To explore reasons for the observed heterogeneity, we performed sensitivity analyses on study characteristics such as study design, measuring instrument, anatomical site, and source of cases and controls, and tested their effects on the relationship between alcohol consumption and cancer of the urinary tract.

Results

Study characteristics

We identified 34 articles on alcohol consumption and the incidence of cancer of the urinary tract published between 1974 and 1997. Usually, the relationship between alcohol consumption and cancer of the urinary tract was not the main research hypothesis. Four studies presented relative risks for ever alcohol consumption with no information on current consumption [14–17]. Ten other articles with mixed results did not provide sufficient information to estimate a summary odds ratio [18–27]. The remaining 20 articles described 16 observational epidemiological studies, which are presented in Table 1 [28–47]. Most studies were carried out in North America or Europe. We included three follow-up studies [34, 42, 47], six population-based case–control studies [30–33, 37–40, 45, 46] and seven hospital-based case–control studies [28, 29, 34–36, 41, 44] in the analyses. The case–control studies also varied with regard to their criteria of case selection. Four case–control studies identified the cancer cases in defined populations [33,

Table 1. Study characteristics of published epidemiological studies concerning current alcohol consumption and cancer of the urinary tract, ordered by year of publication

Ref.	First author	Publication year	Country	Anatomical site of urinary tract	Study design			Alcohol assessment
					Follow-up study	Case–control study		
						Case source	Control source	
28	Morgan	1974	Canada	bladder	–	hospital	hospital	questionnaire*
29	Najem	1982	US	bladder	–	hospital	hospital	interview
30–32	Mommsen†	1982–83	Denmark	bladder	–	hospital	population	both techniques
34	Bravo	1987	Spain	urinary tract	–	hospital	hospital	questionnaire*
35	Iscovich	1987	US	bladder	–	hospital	hospital	interview
36	Brownson	1987	US	bladder	–	population	hospital	questionnaire*
46	Risch	1988	Canada	urinary tract	–	hospital	population	interview
37, 38	Slattery†	1983–88	US	bladder	–	population	population	interview
39	Nomura	1989	US	urinary tract	–	hospital	population	interview
40	Ross	1989	US	renal pelvis†	–	population	population	interview
47	Mills	1991	US	bladder	yes	–	–	questionnaire*
41	D'Avanzo	1992	Italy	bladder	–	hospital	hospital	interview
42	Chyou	1993	Hawaii	urinary tract	yes	–	–	both techniques
43	Murata	1996	Japan	bladder	yes	–	–	questionnaire*
44	Donato	1997	Italy	bladder	–	hospital	hospital	interview
45	Bruemmer	1997	US	bladder	–	population	population	interview

* Self-administered questionnaire.
† Same study had appeared in more than one publication.

36–38, 40, 45], while nine case–control studies selected cases from hospitals [28–32, 34, 35, 39, 41, 44, 46]. Information on alcohol consumption was obtained by interview [29, 33, 35, 37–41, 44–46], self-administered questionnaire [28, 34, 43, 47] or both techniques [30–32, 42]. Some studies included all neoplasms of the urinary tract as cases, of which more than 90% were found to involve bladder cancer [34, 39, 42, 46], while others selected only bladder carcinomas [28–35, 35–38, 41, 43–45, 47] or carcinomas of the renal pelvis and ureter [40]. Most studies used histologically confirmed cases with urothelial cell cancer [28–33, 35–42, 44, 46, 47] (Table 1).

Risk estimation

We could not identify heterogeneity in funnel plots, either visually (Figure 1) or in terms of statistical significance (all p-values ≥ 0.18). Unfortunately, half of the included studies did not provide sufficient information to estimate an adjusted summary odds ratio. The calculation of unadjusted summary odds ratios of cancer of the urinary tract for current alcohol consumers compared to non-drinkers was based on 13 studies. Nine studies allowed calculation of unadjusted odds ratios for men and women combined [28, 29, 33, 35, 37, 39–41, 44, 45]. The odds ratios ranged from 1.0 to 2.4. Some of these studies also presented odds ratios for men and women separately [28, 39, 44, 45]. The remaining studies

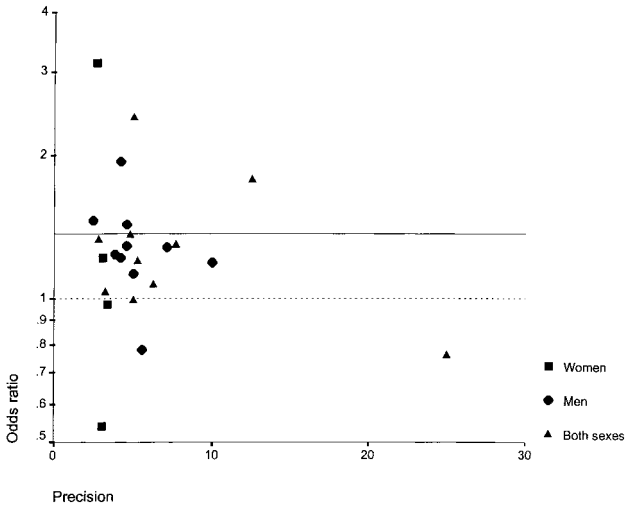

Fig. 1. Funnel plot for current alcohol drinkers *versus* non-drinkers, adjusted. *Interrupted and uninterrupted reference lines indicate no effect and total summary odds ratio, respectively.

only presented sex-specific odds ratios [34, 36, 38, 42, 43, 48]. The unadjusted odds ratios for men and women ranged from 0.8 to 2.0 and from 0.5 to 3.1, respectively. The unadjusted summary odds ratio for nine studies combining men and women was 1.4 (95% CI 1.1–1.6). The sex-stratified unadjusted summary odds ratios were 1.2 (95% CI 1.0–1.5) for nine studies with men and

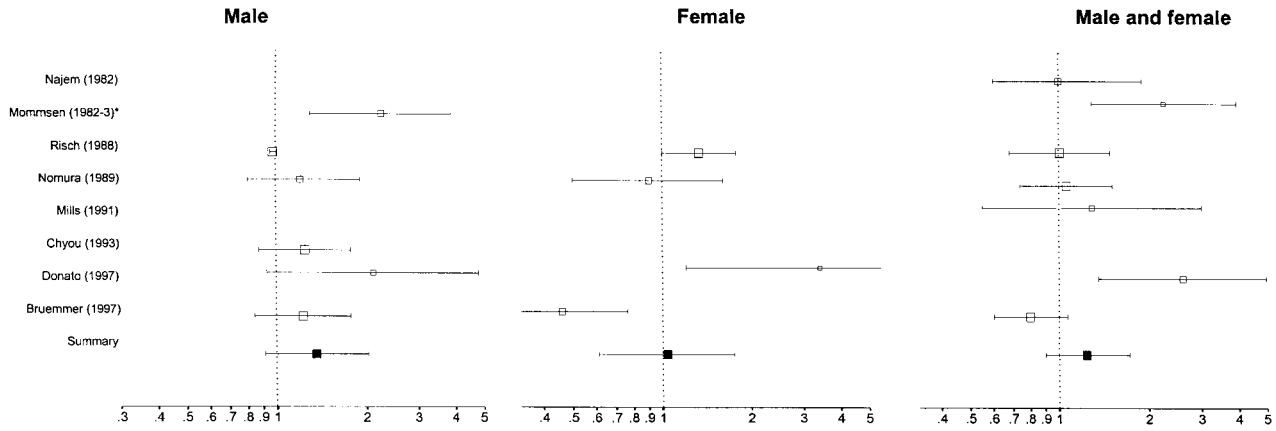

Fig. 2. Adjusted (age, sex, smoking) odds ratios and 95% confidence intervals of cancer of the urinary tract for current alcohol consumers compared to non-drinkers, published in epidemiological studies. * Same study had appeared in more than one publication, reference line indicates no effect, box sizes are proportional to weight study.

1.1 (95% CI 0.7–1.8) for four studies with women (Figure 2). We did not find a statistically significant interaction between alcohol consumption and sex regarding unadjusted odds ratios ($p = 0.77$).

Figure 2 summarizes the adjusted results of observational studies reporting the association between alcohol consumption and the risk of cancer of the urinary tract. Adjusted odds ratios could only be calculated for eight studies, because the exposure-specific prevalence of the non-cases or individual age-, sex- and smoking-adjusted odds ratios were not always available [29–32, 39, 42, 44–47]. Most of the excluded studies did not provide adjusted summary odds ratios with corresponding confidence intervals for current drinkers compared to non-current drinkers. Only one study was excluded because of missing information on the distribution of controls [20]. Frequently used confounders, in addition to age, sex and smoking, were residence [29–32, 39, 42, 45] and race [29, 39]. The adjusted odds ratios of the individual studies ranged from 1.0 to 2.2 and from 0.5 to 3.4 for men and women, respectively. Seven studies contributed to the estimation of a summary odds ratio for men and women combined [29, 31, 39, 44–47]. The adjusted odds ratios ranged from 0.8 to 2.6. The age- and smoking-adjusted summary odds ratios for current alcohol consumption were 1.3 (95% CI 0.9–2.0) for six studies with men and 1.0 (95% CI 0.6–1.7) for four studies with women. For seven studies with men and women combined, the age-, sex- and smoking-adjusted summary odds ratio was 1.2 (95% CI 0.9–1.7) (Figure 2). Sex did not seem to be a statistically significant effect modifier for the adjusted (age and smoking) association between alcohol consumption and cancer of the urinary tract ($p = 0.42$).

Sensitivity analysis

We further examined the crude relationship of alcohol consumption and cancer of urinary tract by study design, measuring instrument, anatomical site and sources of cases and controls (only for case–control studies) to explore their influence on the outcome estimates (Figure 3). All tests for interaction were statistically non-significant. The summary odds ratios for alcohol consumption and cancer of the urinary tract

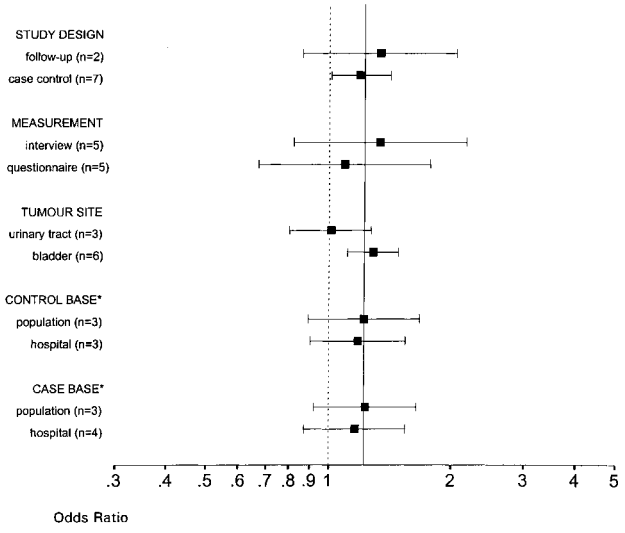

Fig. 3. Crude summary odds ratios and 95% confidence intervals of cancer of the urinary tract for current alcohol consumers compared to non-drinkers by study design, measuring instrument, tumor site and source of cases and controls for nine studies with men. * Only for case control studies; interrupted and uninterrupted reference lines indicate no effect and total summary odds ratio respectively.

were 1.3 (95% CI 0.9–2.0) for follow-up studies and 1.2 (95% CI 1.0–1.4) for case–control studies. The summary odds ratio for studies that used self-administered questionnaires to obtain information on alcohol consumption was 1.1 (95% CI 0.7–1.8). Studies that used interview techniques had a summary odds ratio of 1.3 (95% CI 0.8–2.2). Summary odds ratio were calculated for studies classified according to the anatomical site of the tumor. The summary odds ratio for the relationship between alcohol consumption and cancer of the total urinary tract was 1.0 (95% CI 0.8–1.3). For studies that selected only bladder carcinomas, the summary odds ratio was 1.3 (95% CI 1.1–1.5). Case–control studies that selected cases or controls from defined populations had summary odds ratios of 1.2 (95% CI 0.9–1.6) and 1.2 (95% CI 0.9–1.7), respectively. The summary odds ratios for hospital-based case–control studies were 1.2 (95% CI 0.9–1.5) for studies that selected cases from hospitals and 1.2 (95% CI 0.9–1.5) for studies that selected controls from hospitals.

Discussion

We were able to retrieve 30 articles reporting epidemiological studies on current alcohol consumption and human cancer of the urinary tract. These primary studies can be considered as the best available evidence. Our meta-analysis revealed an approximately 30% elevated risk of cancer of the urinary tract for male alcohol drinkers compared to non-drinkers, although not statistically significant. The risk of cancer of the urinary tract for women in relation to alcohol consumption remains unclear. We expect, however, a similar pattern if more women were included in the original studies.

We did not attempt to uncover unpublished observations and could not include studies with insufficient information to estimate a summary odds ratio. The excluded studies showed mixed results. The estimated effects of alcohol consumption ranged from protective [15, 17, 24], through no effect [16, 25–27] to harmful [14, 18–20, 23]. Three studies did not indicate a direction of the estimated effect [22, 49, 50]. Although publication bias might arise by excluding these studies, we could not identify it in our meta-analysis, neither visually nor in terms of statistical significance.

The definition of "current drinker" at baseline (follow-up studies) or in the reference period (case–control studies) might have caused heterogeneity between studies, because the follow-up period and the reference date varied between the included studies. Therefore, results have to be interpreted with caution. Because of potential additional heterogeneity in populations, designs and analyses of various studies, we assumed that the true effects being estimated would vary between the studies in addition to the usual sampling variation in the estimates (within studies). To account for both sources of variation, we used random effects meta regression analysis to combine the results from the primary studies [13]. The random effect approach provides some allowance for heterogeneity in studies beyond sampling error.

The summary odds ratios were similar across study designs and source of the cases and controls in case-control studies. Although we could not find statistically significant interactions, it appears that the weak elevated risk of cancer for alcohol consumers is mainly confined to cancer of the urinary bladder. The summary odds ratio was higher for studies that used interviewing techniques than for studies that used self-administered questionnaires. This contrast can be a consequence of response bias due to different assessment techniques or to chance alone.

Although 16 studies contributed to this meta-analysis, only eight provided sufficient information to calculated odds ratios, adjusted for at least age, smoking and sex. It was not possible to adjust for a specific set of confounders. Because of the unavailability of adjusted odds ratios in some of the included studies, we also calculated unadjusted odds ratios. Focusing entirely on adjusted odds ratios would have led to the exclusion of 50% of the studies which also have (crude) information on the association between alcohol consumption and cancer of the urinary tract.

Some authors suggested that residual confounding due to tobacco smoking could explain an increased risk for alcohol drinking found in some studies [7, 44]. The adjusted and unadjusted estimates, however, were comparable. Furthermore, a small increased risk was also found among those who stopped smoking [44] and those who claimed to have never smoked [34, 37, 44]. Another explanation for an association between alcohol consumption and cancer of the urinary tract might be that non-drinkers are a rather selected population. In the European Union, 89% of the male population drinks alcohol [51]. Non-drinkers may differ also in occupation; the consumption of coffee, tea, vegetables or fruit; and other lifestyle habits from the general population of drinkers. Age and smoking are currently known to be the most important risk factors for cancer of the urinary tract. However, it remains possible that confounding explains the weak association found in this meta-analysis.

Because of limitations in reported data, the summary odds ratios could not be quantified rigorously on a per-glass basis or subdivided by type of alcoholic beverage. Nine of the included articles only provided odds ratios

for current drinking *versus* non-drinking [28–32, 38, 41, 46, 47]. The remaining articles provided data within different exposure categories [33–37, 39, 40, 42–45]. The content of these categories, however, differed substantially between the studies. In this meta-analysis, we therefore compared current alcohol consumption with no alcohol consumption. The associations between the consumption of specific alcoholic beverages (beer, wine or spirits) and the risk of cancer of the urinary tract were reported in nine studies with no consistent results [14, 20, 24, 33, 35, 40–42, 46].

We conclude that current alcohol consumption slightly increases the risk of male cancer of the urinary tract by approximately 30%. The risk of cancer of the urinary tract related to alcohol consumption for women and the influence of the amount and type of alcohol remains unclear.

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