



# Impact of alcohol consumption on the risk of developing bladder cancer: a systematic review and meta-analysis

Mihai Dorin Vartolomei<sup>1,2</sup> · Takehiro Iwata<sup>1,3</sup> · Beat Roth<sup>4</sup> · Shoji Kimura<sup>1,5</sup> · Romain Mathieu<sup>1,6</sup> · Matteo Ferro<sup>7</sup> · Shahrokh F. Shariat<sup>1,8,9,10,11</sup> · Christian Seitz<sup>1</sup>

Received: 31 December 2018 / Accepted: 27 May 2019  
© Springer-Verlag GmbH Germany, part of Springer Nature 2019

## Abstract

**Background** Epidemiologic studies that investigated alcohol consumption in relation to the risk of bladder cancer (BCa) have demonstrated inconsistent results. We conducted a systematic review and meta-analysis of the literature to investigate the association of alcohol including different types of alcoholic beverages consumption with the risk of BCa.

**Materials and methods** A systematic search of Web of Science, Medline/PubMed and Cochrane library was performed in May 2018. Studies were considered eligible if they assessed the risk of BCa due to alcohol consumption (moderate or heavy dose) and different types of alcoholic beverages (moderate or heavy dose) in multivariable analysis in the general population (all genders, males or females) or compared with a control group of individuals without BCa. Study design: observational cohorts or case–control.

**Results** Sixteen studies were included in this meta-analysis. Moderate and heavy alcohol consumption did not increase the risk of BCa in the entire population. Sub-group and sensitivity analyses revealed that heavy alcohol consumption increased significantly the risk of BCa in the Japanese population, RR 1.31 (95% CI 1.08–1.58,  $P < 0.01$ ) in the multivariable analysis, and in males RR of 1.50 (95% CI 1.18–1.92,  $P < 0.01$ ), with no significant statistical heterogeneity. Moreover, heavy consumption of spirits drinks increased the risk of BCa in males, RR 1.42 (95% CI 1.15–1.75,  $P < 0.01$ ).

**Conclusion** In this meta-analysis, moderate and heavy alcohol consumption did not increase the risk of bladder cancer significantly. However, heavy consumption of alcohol might increase the risk of BCa in males and in some specific populations.

**Keywords** Alcohol consumption · Cancer risk · Bladder cancer

## Introduction

Bladder cancer (BCa) was the 12th most commonly diagnosed malignancy worldwide in 2018 with an estimated 550,000 new cases and 200,000 deaths [1]. Among the most important epidemiological factors for BCa are gender [2, 3, 4], cigarette smoking [4] and occupational exposure to aromatic amines [5–7]. The role of dietary factors such as

alcohol consumption has also been investigated, but the evidence remains unclear [8]. However, it seems that a Mediterranean diet has a protective role when eliminating fats and alcohol intake [9].

A previous meta-analysis, including 16 case–control studies and 3 cohort studies, showed no association of alcohol consumption with the risk of BCa [10]. Since the meta-analysis was published, epidemiologic studies of alcohol consumption in relation to the risk of BCa have reported inconsistent results. Recently, a large prospective cohort study investigated the association of different types of alcoholic beverage consumption as well as alcohol consumption with the risk of BCa. The authors reported that high intakes of spirits were associated with an increased risk of BCa in men and smokers [11]. Regarding, upper tract urothelial carcinoma (UTUC) there have been little data available regarding alcohol consumption and its role in cancer development [12].

**Electronic supplementary material** The online version of this article (<https://doi.org/10.1007/s00345-019-02825-4>) contains supplementary material, which is available to authorized users.

Mihai Dorin Vartolomei and Takehiro Iwata equal contribution as first author.

✉ Shahrokh F. Shariat  
shahrokh.shariat@meduniwien.ac.at

Extended author information available on the last page of the article

We hypothesized that alcohol intake can have an impact on the risk of BCa development. Therefore, we conducted a systematic review and meta-analysis of the literature to investigate the association of alcohol including different types of alcoholic beverage consumption with the risk of BCa.

## Materials and methods

### Protocol

The protocol was registered in the International Prospective Register of Systematic Reviews database (PROSPERO: CRD42018093472). The meta-analysis was conducted following the guidelines developed by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group [13]. In May 2018, two investigators (MDV and TI) carried out a systematic literature search of Web of Science, Medline/PubMed and Cochrane library using the terms “alcohol” AND “bladder cancer”. All original articles that fulfilled the inclusion criteria listed above were included, without any restriction of date and language of publications.

### Inclusion and exclusion criteria

Studies were considered eligible if they assessed the risk of BCa due to alcohol consumption (moderate or heavy dose) and different types of alcoholic beverages (moderate or heavy dose) in multivariable analysis in the general population (all genders, males or females) or compared with a control group of individuals without BCa. Study design: observational cohorts or case–control. Good-quality studies according to Newcastle–Ottawa Scale (NOS) [14] and Agency for Health Research and Quality (AHRQ) standards were included.

For each included study, the following items were extracted from the full text by two investigators: first author’s name, year of publication, country, study type, number of patients, and variables used in the multivariable analysis, reported odds ratios (ORs), risk ratios (RRs) or hazard ratios (HRs) for BCa and their confidence interval (CI) in multivariable analysis for each reported dose of alcohol (moderate or heavy) and follow-up in case of cohort studies.

### Study quality and risk of bias evaluation

Study quality was determined by the NOS [14] for cohort studies. Thresholds for converting the NOS to AHRQ standards: good quality: three or four stars in the selection domain AND one or two stars in the comparability domain AND two or three stars in the outcome/exposure domain; fair quality: two stars in the selection domain AND one or two stars in

the comparability domain AND two or three stars in the outcome/exposure domain; poor quality: zero or one star in the selection domain OR zero stars in the comparability domain OR zero or one star in the outcome/exposure domain. Sixteen studies with good quality according to a duplicate analysis were included in the meta-analysis (Supplementary material 1A).

The “risk-of-bias” (RoB) evaluation of each study was assessed according to the Cochrane Handbook for Systematic Reviews of interventions for including non-randomized studies [15]. Due to only non-randomized comparative studies, RoB was determined by examining the risk of pre-assigned confounders. The main confounding factors were age, sex, smoking status, socioeconomic status and occupation. We, therefore, reviewed the studies adjusting for these confounders within their used Cox regression analysis. The presence of confounders was determined by consensus (Supplementary material 1B).

A total of 2348 abstracts and titles were initially identified. After removal of duplicates, 830 remained. Then, 775 articles were excluded after screening titles and abstracts. We assessed 55 full text articles; 33 studies were included for the qualitative synthesis [11, 16–47], from which 16 were quantitative synthesis (meta-analysis) [11, 22, 23, 26–28, 33, 36–39, 41, 43, 45–47] (Fig. 1).

### Statistical analysis

First, we performed a formal meta-analysis for risk of BCa according to the quantity of alcohol consumed (moderate and heavy consumption). Second, we performed a formal meta-analysis for risk of BCa according to heavy alcohol consumption and region of the population. Third, we performed a formal meta-analysis for risk of BCa in males according to the type of alcohol and quantity of alcohol consumed (heavy consumption). Fourth, we performed a formal meta-analysis for risk of BCa according to the gender and quantity of alcohol consumed (heavy consumption). Grams of ethanol were used as measure for the analyses, defining one drink as 10 g of ethanol, if not otherwise specified in the original report. We used non-drinkers as reference. We defined moderate alcohol intake as  $\leq 30$  g of ethanol per day or drinking alcohol even a little, and heavy alcohol intake as the most heavy volume of ethanol. The alcohol intake in each study ranged from  $> 30$  to 150 g. ORs, RRs and HRs with their 95% CIs reported from each study were used to calculate RRs [48], considering a baseline risk of 0.01. Pooled RRs estimates were calculated with the fixed-effect or random-effect model in case of significant heterogeneity. Statistical heterogeneity was defined based on Cochrane  $I^2$  statistics. To evaluate publication bias, Egger linear regression [49] and funnel plots were examined. We conducted sensitivity analyses by excluding each study and

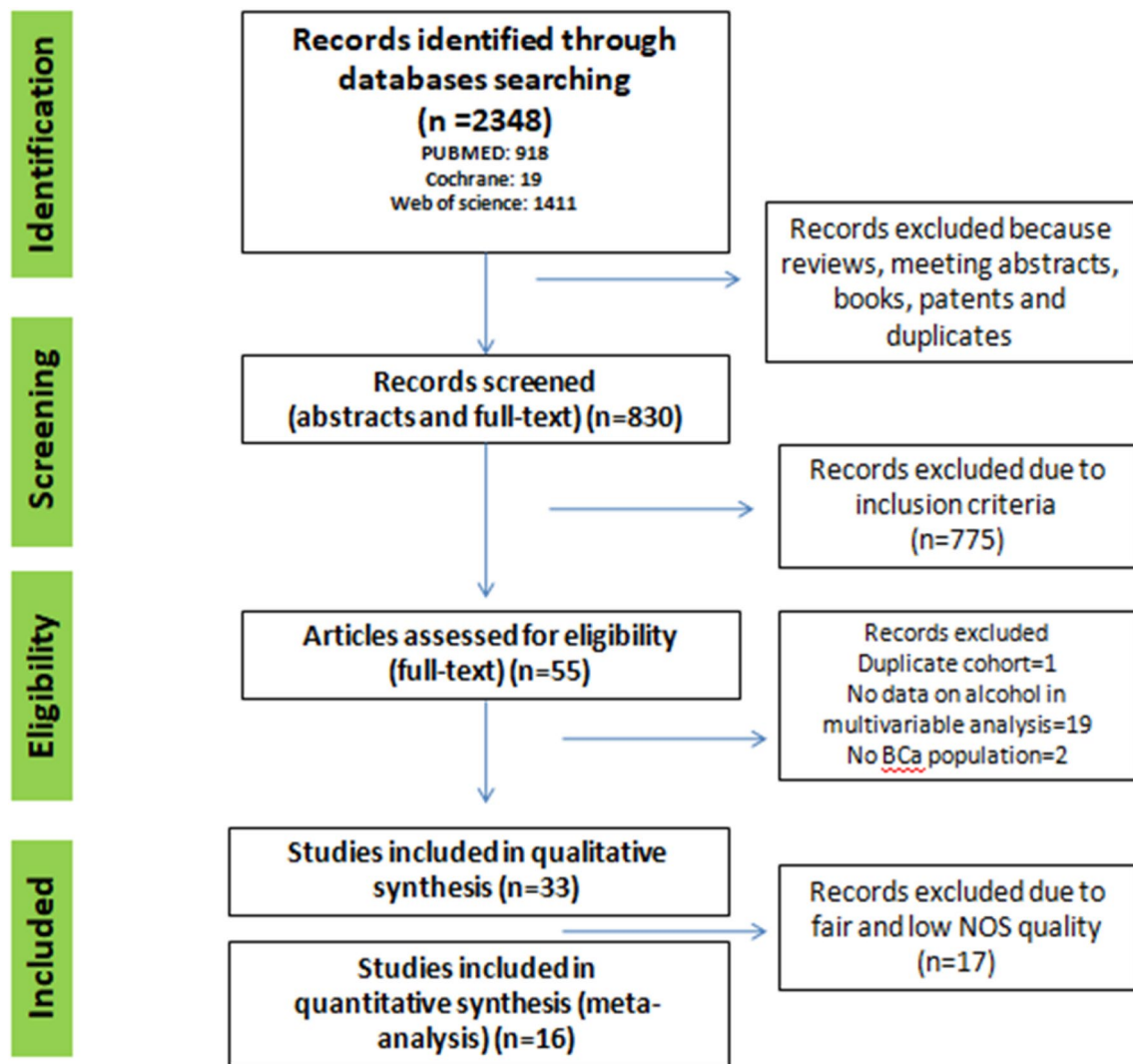


Fig. 1 PRISMA flowchart of the study selection process

the results presented did not change, except in case of heavy consumption of alcohol in males.  $P$  values  $< 0.05$  were considered statistically significant. Statistical analyses were performed using Stata 14.0 statistical software (Stata Corp., College Station, TX, USA).

## Results

### Moderate alcohol consumption and BCa risk

Nine studies (630,037 subjects) fulfilled the inclusion criteria regarding moderate alcohol consumption and the risk of BCa (4 cohort and 5 case–control studies) (Table 1). The pooled RR for the risk of BCa was 0.97 (95% CI 0.88–1.07,  $P = 0.59$ ) in the multivariable analysis (Fig. 2a). The Cochrane's  $Q$  test ( $\chi^2 = 5.15$ ;  $P = 0.74$ ) and  $I^2$  test ( $I^2 = 0\%$ )

did not show a significant heterogeneity. The funnel plot did not identify studies over the pseudo 95% CI with Egger test:  $P = 0.68$  (Fig. 2a). Furthermore, we performed sub-analyses according to the region of the population, gender and type of alcoholic beverages and the results remained similar (Fig. 3a, data shown for Japan).

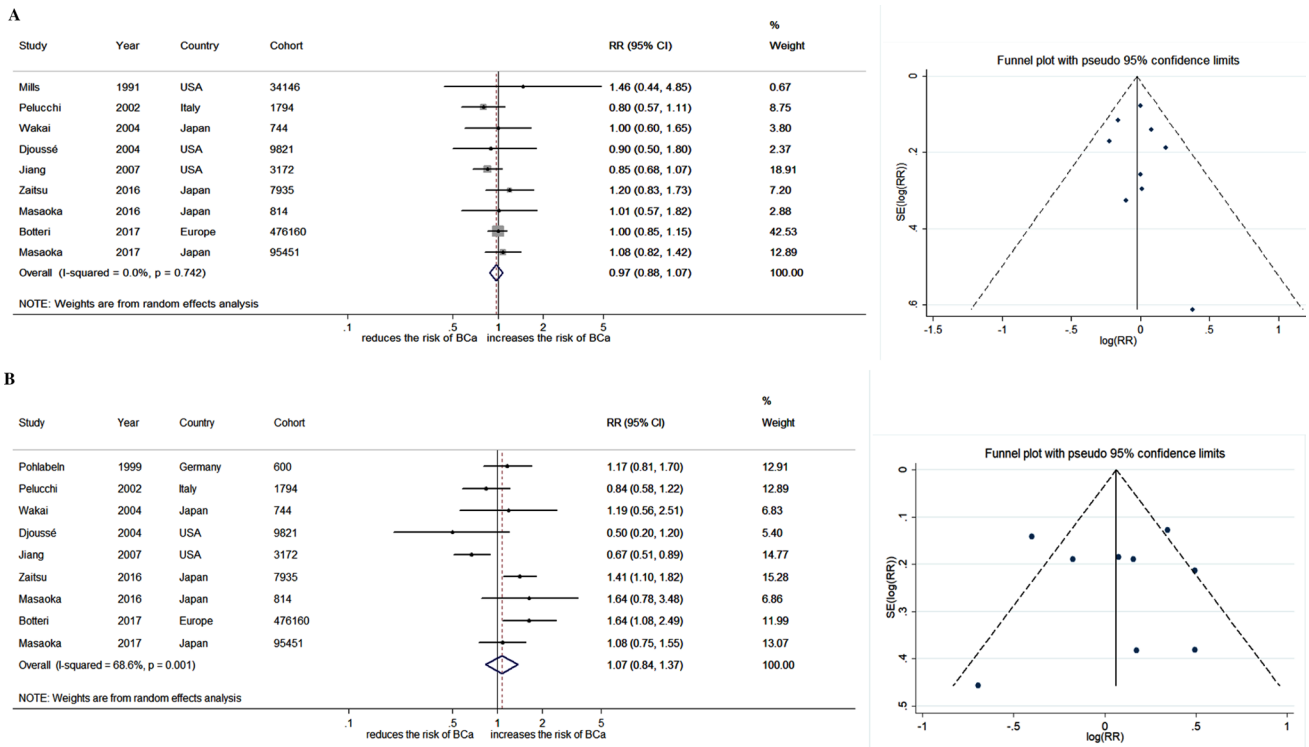
### Heavy alcohol consumption and BCa risk

Nine studies (596,491 subjects) fulfilled the inclusion criteria regarding heavy alcohol consumption and the risk of BCa (3 cohort and 6 case–control studies). The pooled RR for the risk of BCa was 1.07 (95% CI 0.84–1.37,  $P = 0.58$ ) in the multivariable analysis (Fig. 2b). The Cochrane's  $Q$  test ( $\chi^2 = 25.44$ ;  $P < 0.01$ ) and  $I^2$  test ( $I^2 = 68.6\%$ ) showed a significant heterogeneity. The funnel plot identified two studies over the pseudo 95% CI with Egger test:  $P = 0.99$  (Fig. 2b).

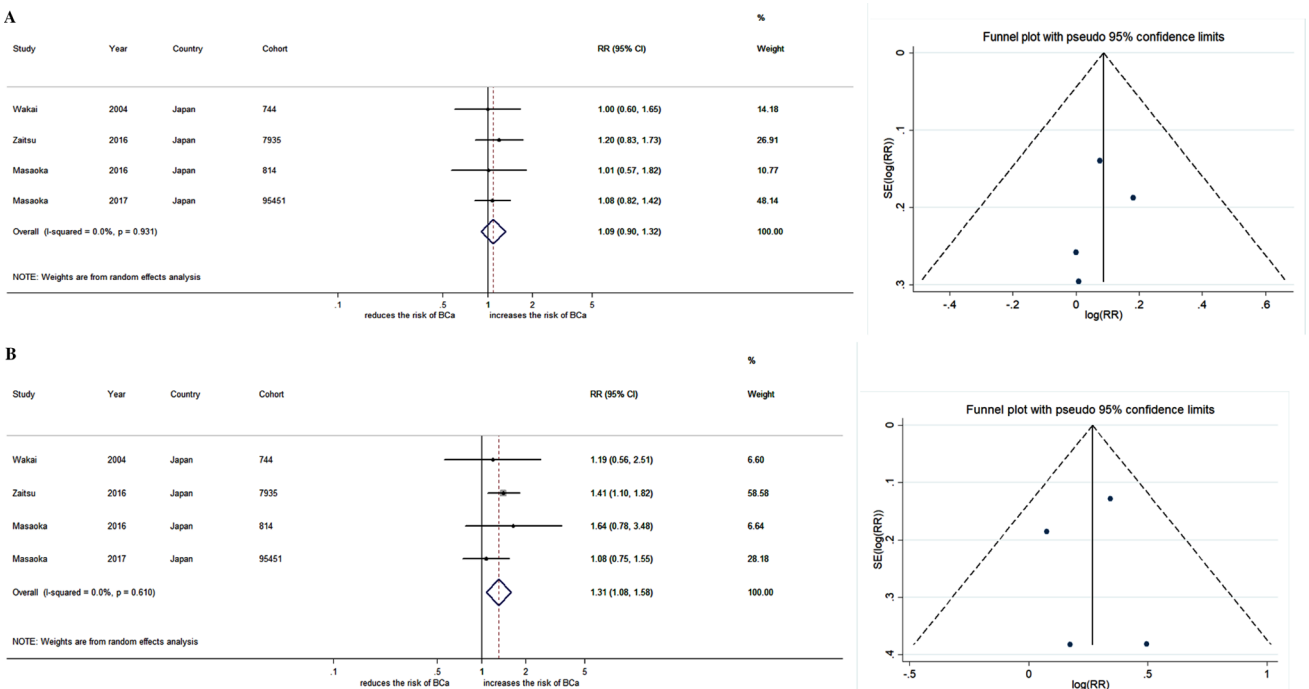
**Table 1** Studies with good quality according to NOS that investigated the impact of alcohol consumption (moderate and heavy) on the risk of bladder cancer and included in the meta-analysis

No.	Study	Year	Country	Study type	N control Male	N BCa Male	Moderate dose (alcohol)	RR (CI) Alcohol and risk of BCa	Heavy dose (alcohol)	RR (CI) Alcohol and risk of BCa	Follow-up (years)	Variables
1	Mills	1991	USA	Cohort	34,146	52	≥ 1 drinks/week	1.46 (0.44–4.85)	–	–	–	Age, sex, smoking
2	Pohlabeih	1999	Germany	Case-control	300	300	–	–	> 20 g/day	1.17 (0.81–1.7)	–	Smoking
3	Pelucchi	2002	Italy	Case-control	1067	727	< 3 drinks/day	0.8 (0.57–1.11)	> 6 drinks/day	0.84 (0.58–1.22)	–	Age, sex, study center, education, smoking habits, coffee, tea, green vegetable intake, occupation
4	Wakai	2004	Japan	Case-control	620	124	< 22 g/day	1 (0.6–1.65)	> 66 g/day	1.19 (0.56–2.51)	–	Age, sex, year of first visit, smoking
5	Djoussé	2004	USA	Cohort	9821	126	< 6 g/day	0.9 (0.5–1.8)	> 48 g/day	0.5 (0.2–1.2)	27.3	Age, sex, smoking, other beverage types
6	Jiang	2007	USA	Case-control	1586	1586	< 13 g/day	0.85 (0.68–1.07)	> 52 g/day	0.67 (0.51–0.89)	–	Level of education, use of NSAIDs, carotenoid intake, number of years as hairdresser/barber, smoking, intake of all other beverages (water, coffee, tea, milk, juice, hot chocolate, soda)
7	Zaitu	2016	Japan	Case-control	7196	739	< 15 g/day	1.2 (0.83–1.73)	> 30 g/day	1.41 (1.1–1.82)	–	Alcohol intensity, smoking, occupation, comorbidities
8	Masaoka	2016	Japan	Case-control	740	74	< 46 g/day	1.01 (0.57–1.82)	> 46 g/day	1.64 (0.78–3.48)	–	Age, sex, smoking
9	Botteri	2017	EU	Cohort	476,160	1802	> 6–12 (M) > 3–12 (F) g/day	1 (0.85–1.15)	> 96 (M) > 60 (F) g/day	1.64 (1.08–2.49)	13.9	Age, sex, center, smoking, energy intake, body mass index, physical activity, educational level
10	Masaoka	2017	Japan	Cohort	95,451	464	1–150 g/week	1.08 (0.82–1.42)	> 450 g/week	1.08 (0.75–1.55)	18.2	Age, sex, area, smoking status

CI confidence interval, EU European Union, F female, M male, N number of patients, RR risk ratio, UK United Kingdom, USA United States of America



**Fig. 2** Forest and funnel plots for the risk of bladder cancer in the case of moderate **a** and heavy **b** consumption of all types of alcohol (all genders included)



**Fig. 3** Forest and funnel plots for the risk of bladder cancer in the case of moderate **a** and heavy **b** consumption of all types of alcohol in the Japanese population (all genders included)

Furthermore, we performed subgroup analyses according to the region of the population included and results were similar showing no impact of heavy alcohol consumption on BCa risk, except when we analyzed the four studies (1 cohort and 3 case-control studies; 104,944 subjects) from Japan. The pooled RR for the risk of BCa was 1.31 (95% CI 1.08–1.58,  $P < 0.01$ ) in the multivariable analysis (Fig. 3b). The Cochrane's  $Q$  test ( $\chi^2 = 1.82$ ;  $P = 0.61$ ) and  $I^2$  test ( $I^2 = 0\%$ ) showed no significant heterogeneity. The funnel plot did not identify any studies over the pseudo 95% CI with Egger test:  $P = 0.92$  (Fig. 3b).

## Gender

Five studies (3 cohort and 2 case-control studies; 156,245 males) fulfilled the inclusion criteria regarding heavy alcohol consumption and risk of BCa in males (Table 2). The pooled RR for the risk of BCa was 1.27 (95% CI 0.9–1.79,  $P = 0.17$ ) in the multivariable analysis (Fig. 4a). The Cochrane's  $Q$  test ( $\chi^2 = 11.28$ ;  $P = 0.02$ ) and  $I^2$  test ( $I^2 = 64.5\%$ ) showed a significant heterogeneity. The funnel plot identified one study over the pseudo 95% CI with Egger test:  $P = 0.25$  (Fig. 4a). At sensitivity analyses when excluding Brownson et al.'s study [22], the pooled RR was 1.5 (95% CI 1.18–1.92,  $P < 0.01$ ) in the multivariable analysis (Fig. 4b). With no significant heterogeneity: Cochrane's  $Q$  test ( $\chi^2 = 1.24$ ;  $P = 0.74$ ) and  $I^2$  test ( $I^2 = 0\%$ ) and no study over the 95% CI on funnel plot with Egger test:  $P = 0.85$  (Fig. 4b).

Three studies (2 cohort and 1 case-control studies; 1,617,848 females) fulfilled the inclusion criteria regarding heavy alcohol consumption and risk of BCa in females (Table 3). The pooled RR for the risk of BCa was 0.87 (95% CI 0.69–1.09,  $P = 0.22$ ) in the multivariable analysis (Fig. 4c). The Cochrane's  $Q$  test ( $\chi^2 = 0.33$ ;  $P = 0.84$ ) and  $I^2$  test ( $I^2 = 0\%$ ) showed a significant heterogeneity. The funnel plot showed no study over the pseudo 95% CI with Egger test:  $P = 0.13$  (Fig. 4c). Sensitivity analyses did not show different results.

## Alcoholic beverages

Eight studies fulfilled the inclusion criteria regarding heavy consumption of wine, beer or spirits and risk of BCa in males (Table 4). The pooled RRs for the risk of BCa in males due to heavy consumption of wine, beer and spirits were 0.99 (95% CI 0.79–1.24,  $P = 0.9$ ), 1.11 (95% CI 0.7–1.77,  $P = 0.65$ ) and 1.42 (95% CI 1.15–1.75,  $P < 0.01$ ), respectively, in multivariable analyses (Fig. 5a–c). The Cochrane's  $Q$  test ( $\chi^2 = 3.79$ ;  $P = 0.7$ ,  $\chi^2 = 25.4$ ;  $P < 0.01$ ,  $\chi^2 = 5.72$ ;  $P = 0.33$ ) and  $I^2$  test ( $I^2 = 0.0\%$ ,  $I^2 = 76.4\%$ ,  $I^2 = 12.6\%$ ), respectively, showed a significant heterogeneity in the beer group. The funnel plots did not identify any studies over the pseudo 95% CI in both wine and spirits

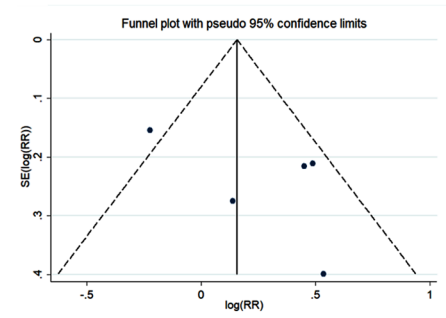
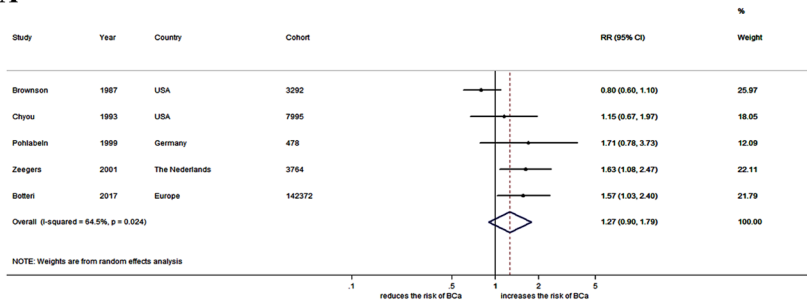
**Table 2** Studies with good quality according to NOS that investigated the impact of heavy alcohol consumption on the risk of bladder cancer in males and included in meta-analysis

No.	Study	Year	Country	Study type	N Control	N BCa	Heavy dose (alcohol)	RR (CI)	Follow-up (years)	Variables
1	Brownson	1987	USA	Case-control	2469	823	> 2 drinks/day	0.8 (0.6–1.1)	–	Age, smoking
2	Chyou	1993	USA	Cohort	7995	96	≥ 15 g/day	1.15 (0.67–1.97)	19	Age, smoking
3	Pohlhabeln	1999	Germany	Case-control	239	239	> 41 g/day	1.71 (0.78–3.73)	–	smoking
4	Zeegers	2001	The Netherlands	Cohort	3170	517	> 30 g/day	1.63 (1.08–2.47)	6.3	Age, smoking
5	Botteri	2017	EU	Cohort	142,372	1273	> 96 g/day	1.57 (1.03–2.4)	13.9	Age, sex, center, smoking, energy intake, body mass index, physical activity, educational level

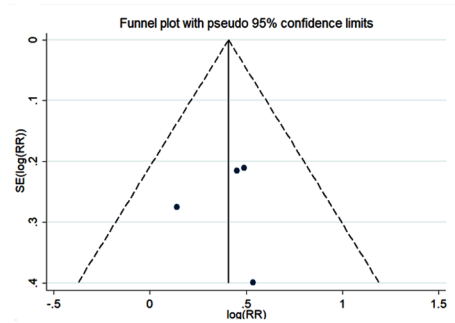
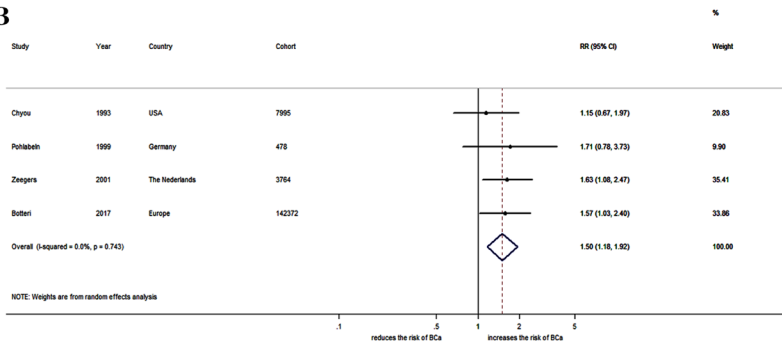
CI: confidence interval, N: number of patients, RR: risk ratio, USA: United States of America EU: European Union, NOS: Newcastle–Ottawa Scale



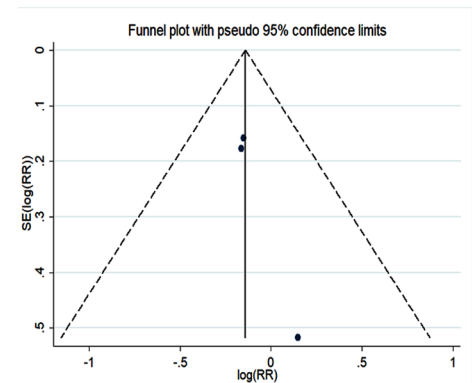
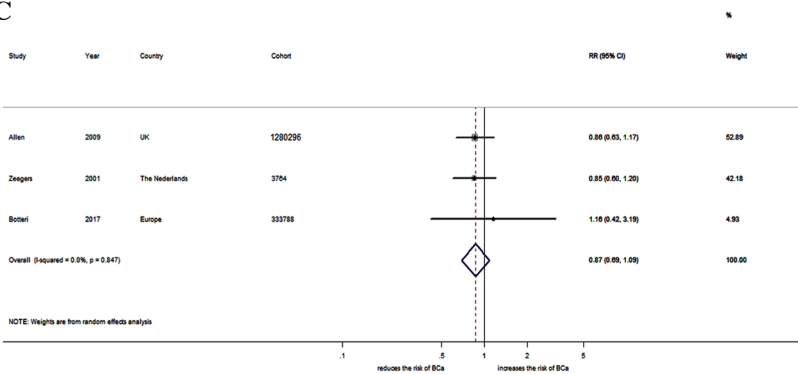
A



B



C



**Fig. 4** Forest and funnel plots for the risk of bladder cancer in case of heavy consumption of all types of alcohol **a** male, **b** male without Brownson et al. study and **c** female

groups; in beer group, three studies were identified over the pseudo 95% CI with Egger test: ( $P=0.18$ ,  $P=0.57$ ,  $P=16$ ), respectively (Fig. 5a–c). Sensitivity analyses did not show a change in the results.

### Discussion

According to this meta-analysis that included data coming from 16 studies published during a 40-year period, alcohol consumption does not significantly affect the risk of developing BCa, when considering the general population. In subgroup analyses, we found that heavy consumption of any type of alcohol increases the risk in specific populations

(Japanese) of developing BCa by 31%. Moreover, in males, heavy consumption of spirits increases the risk by 42% (RR 1.42) compared to non-drinkers.

Alcohol drinking and BCa risk represent an ardent topic of interest within the urologic community. Most of the studies published in the last 40 years had focused on alcohol consumption and BCa risk, with only one recent case–control study [12] that investigated the association regarding risk of upper tract urothelial carcinoma (UTUC). The authors demonstrated in a Japanese population that heavy alcohol consumption > 30 g/day, increases the risk of developing UTUC by 26%; however, further studies must confirm their findings. In the current meta-analysis, we found similar association also regarding heavy alcohol consumption and risk of BCa in the Japanese population compared to non-drinkers.

**Table 3** Studies with good quality according to NOS that investigated the impact of heavy alcohol consumption on the risk of bladder cancer in females and included in meta-analysis

No.	Study	Year	Country	Study type	N Control	N BCa	Heavy dose (alcohol)	RR (CI)	Follow-up (years)	Variables
1	Allen	2009	UK	Cohort	1,280,296	928	≥15 drinks/week	0.86 (0.63–1.17)	7.2	Age, region of residence, socioeconomic status, body mass index, smoking, physical activity, use of oral contraceptives, hormone replacement therapy
2	Zeegers	2001	The Netherlands	Cohort	3170	77	> 30 g/day	0.85 (0.6–1.2)	6.3	Age, smoking
3	Botteri	2017	EU	Cohort	333,788	529	> 60 g/day	1.16 (0.42–3.19)	13.9	Age, sex, center, smoking, energy intake, body mass index, physical activity, educational level

CI confidence interval, N number of patients, RR risk ratio, UK United Kingdom, EU European Union, NOS Newcastle–Ottawa Scale

**Table 4** Studies with good quality according to NOS that investigated the impact of heavy alcohol consumption (wine, beer and spirits) on the risk of bladder cancer in males included in the meta-analysis

No.	Study and year	N Control Male	N BCa Male	heavy dose (wine)	RR (CI) <sup>a</sup> Wine and risk of BCa	Heavy dose (beer)	RR (CI) <sup>a</sup> Beer and risk of BCa	Heavy dose (spirits)	RR (CI) <sup>a</sup> Spirits and risk of BCa
1	Kunze 1992	675 531	675 531	> 0.3 L/day	1 (0.4–2.3)	> 1 L/day	2.5 (1.3–4.6)	> 0.5 L/day	2.1 (0.9–4.5)
2	Chyou 1993	7995 7995	96 96	–	–	> 250 g/day	1.13 (0.67–1.92)	> 2 g/day	1.67 (0.98–2.84)
3	Pohlabeln 1999	300 239	300 239	≥ 3 glass/day	2.48 (0.41–14.89)	≥ 3 bottle/day	1.82 (0.79–4.21)	–	–
4	Zeegers 2001	3170 1591	594 517	≥ 30 g/day	1.73 (0.74–4.05)	≥30 g/day	1.09 (0.46–2.57)	≥30 g/day	1.94 (1.17–3.22)
5	Pelucchi 2002 <sup>b</sup>	1067 769	727 617	≥ 5 drinks/day	0.86 (0.6–1.23)	–	–	–	–
6	Djoussé 2004 <sup>b</sup>	9821 n.a	126 n.a	> 4 dr/week	0.8 (0.4–1.7)	> 4 dr/week	0.5 (0.2–0.8)	> 4 dr/week	1.6 (0.9–3.1)
7	Jiang 2007 <sup>b</sup>	1586 1225	1586 1228	> 52 g/day	0.91 (0.41–2.02)	>52 g/day	0.54 (0.35–0.83)	>52 g/day	1.01 (0.63–1.62)
8	Botteri 2017 <sup>b</sup>	476,160 142,372	1802 1273	> 60 g/day	1.08 (0.71–1.65)	>60 g/day	1.56 (0.99–2.46)	>24 g/day	1.23 (0.91–1.66)

CI confidence interval, N number of patients, RR risk ratio, NOS Newcastle–Ottawa Scale

<sup>a</sup>Adjusted for age and smoking

<sup>b</sup>Included more than 85% males

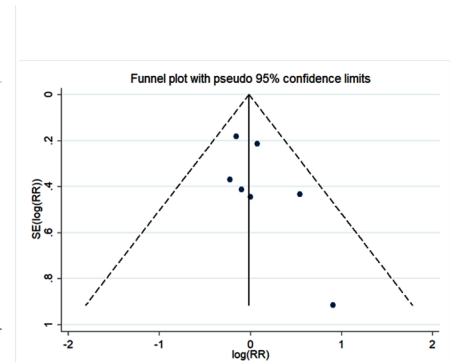
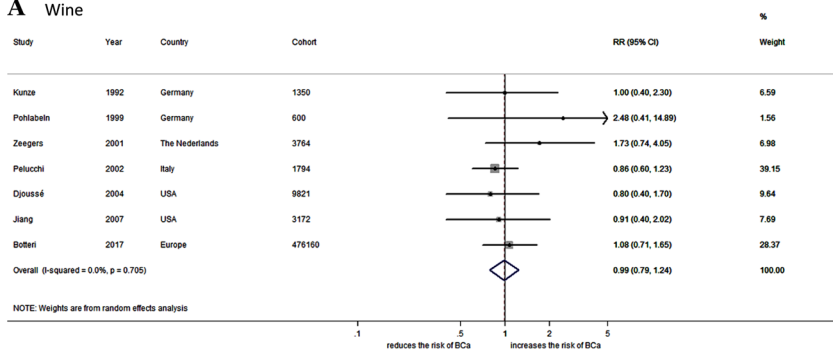
Moreover, heavy alcohol consumption might increase the risk of BCa up to 50% in males according to our sensitivity analyses. This results are in contrast with those reported by the previous meta-analysis [10] that included 19 studies published until 2010 and showed no difference in risk compared with non-drinkers; the pooled RR of BCa was 1.00 (95% CI 0.92–1.09) for moderate and 1.02 (95% CI

0.78–1.33) for heavy alcohol drinkers. In the current meta-analysis, compared to the aforementioned study, we analyzed also the effect of alcohol consumption on BCa risk according to the type of alcohol consumed and we included only good-quality studies according to NOS.

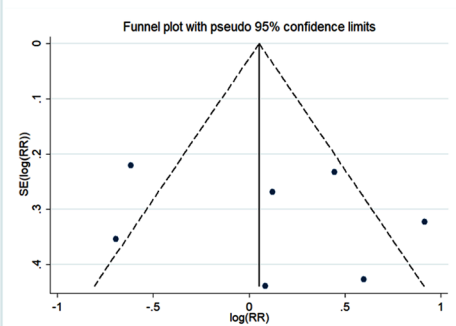
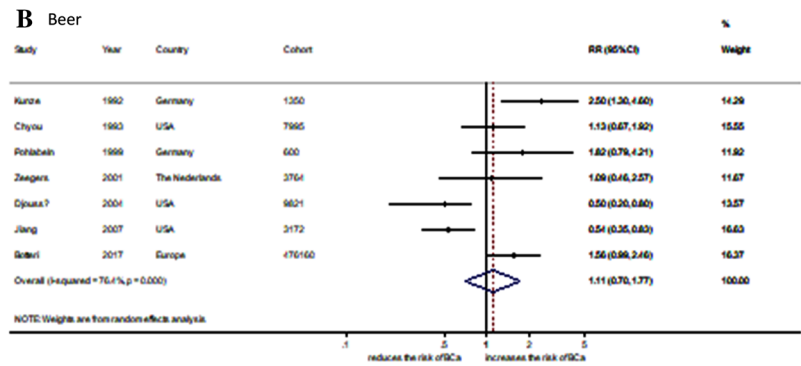
A possible role of alcohol in the etiology of BCa is due to its metabolite acetaldehyde which is excreted through the



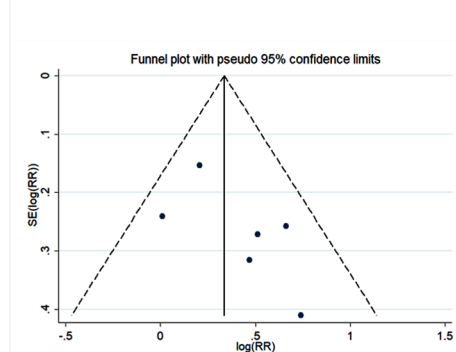
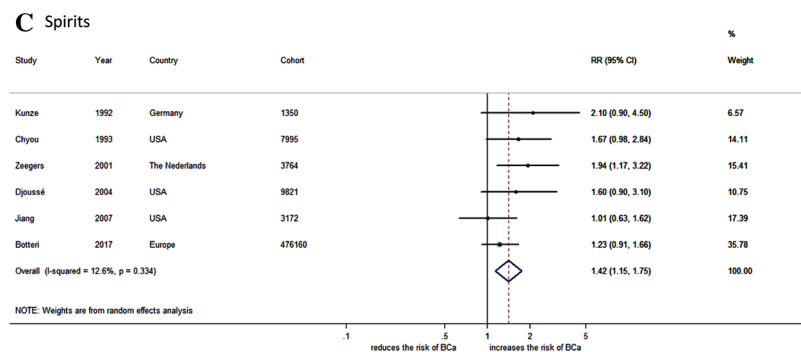
**A** Wine



**B** Beer



**C** Spirits



**Fig. 5** Forest and funnel plots for the risk of bladder cancer in the case of heavy consumption of several drinks: **a** wine, **b** beer and **c** spirits, in males

urinary tract [50]. Acetaldehyde seems to cause damage to the DNA and is classified as carcinogenic to humans [51]. However, the exposure of the kidney and bladder urothelium to this carcinogen is low, as alcoholic beverages have a diuretic effect which leads to higher frequency of micturition [53]. We further did not see an increased risk with advancing age (data not shown) which is often associated with lower urinary tract symptoms in males, leading to longer intravesical exposure of urine. Regarding the effect of alcohol exposure in different population, it was demonstrated that there are some polymorphisms of genes encoding alcohol-metabolizing enzymes in Japanese populations which are different from those in Western populations and

these differences might account for the higher prevalence of alcohol-related cancers such as esophageal cancer in Japanese populations [52]. Since the carcinogenesis frequently occurs through the influence of environmental and genetic factors, the impact of heavy alcohol drinking on BCa risk in Japanese populations may be different from that in Western populations.

Tobacco smoking is known as the most important lifestyle risk factor for BCa [54, 55]. It is, in some populations, associated with alcohol drinking [56]. In all studies, the risk of BCa due to alcohol consumption was adjusted for the effects of smoking status in the multivariable analyses; the pooled RRs of our meta-analysis revealed an increased risk

of BCa in males that suffered heavy exposure to alcohol, especially spirits of 42%. In contrast to our findings, in the previous meta-analysis, the pooled RR was 0.98 (95% CI 0.89–1.07) for moderate and 0.97 (95% CI 0.72–1.31) for heavy drinking [10]. However, the previous study suffered from lower quality of included studies and patient numbers.

Even if we included only good-quality studies, our study has several limitations. First, there is a selection bias in the studies, as all were non-randomized observational or case–control studies. Second, the definition of consumption was not standardized with wide differences between studies introducing heterogeneous results; however, there was no statistical heterogeneity between studies in statistical significant results. Third, it seems that risk is influenced by race and other lifestyle habits that are often not or incompletely recorded.

## Conclusions

In this meta-analysis, moderate and heavy alcohol consumption did not increase the risk of bladder cancer significantly. However, heavy consumption of alcohol might increase the risk of BCa in males and in some specific populations. BCa prevention campaigns should include alcohol cessation programs besides smoking cessation programs as it may increase the risk of BCa in addition to causing many other diseases.

**Acknowledgements** M.D.V had an EUSP lab/clinical fellowship awarded by EAU (European Association of Urology) and an Ernst Mach Grant awarded by OeAD, Austria.

**Author contribution** Protocol/project development: MDV, TI, BR, SK, RM, MF, SFS, CS. Data collection or management: MDV, TI, BR, SK, RM, MF, SFS, CS. Data analysis: MDV, TI, BR, SK, RM, MF, SFS, CS. Manuscript writing/editing: MDV, TI, BR, SK, RM, MF, SFS, CS.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Informed consent** For this type of study formal consent is not required.

**Human and animal rights** This article does not contain any studies with human participants or animals performed by any of the authors.


## References

- Bray F, Ferlay J, Soerjomataram I et al (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 68:394–424. <https://doi.org/10.3322/caac.21492>
- Dobruch J, Daneshmand S, Fisch M et al (2016) Gender and bladder cancer: a collaborative review of etiology, biology, and outcomes. *Eur Urol* 69:300–310. <https://doi.org/10.1016/j.eururo.2015.08.037>
- Lucca I, Klatter T, Fajkovic H et al (2015) Gender differences in incidence and outcomes of urothelial and kidney cancer. *Nat Rev Urol* 12:585–592. <https://doi.org/10.1038/nrurol.2015.232>
- Rink M, Crivelli JJ, Shariat SF et al (2015) Smoking and bladder cancer: a systematic review of risk and outcomes. *Eur Urol Focus* 1:17–27. <https://doi.org/10.1016/j.euf.2014.11.001>
- Rouprêt M, Babjuk M, Compérat E et al (2015) European association of urology guidelines on upper urinary tract urothelial cell carcinoma: 2015 update. *Eur Urol* 68:868–879. <https://doi.org/10.1016/j.eururo.2015.06.044>
- Babjuk M, Böhle A, Burger M et al (2017) EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2016. *Eur Urol* 71:447–461. <https://doi.org/10.1016/j.eururo.2016.05.041>
- Mathieu R, Vartolomei MD, Mbeutcha A et al (2016) Urothelial cancer of the upper urinary tract: emerging biomarkers and integrative models for risk stratification. *Minerva Urol Nefrol Ital J Urol Nephrol* 68:381–395
- Fankhauser CD, Mostafid H (2018) Prevention of bladder cancer incidence and recurrence: nutrition and lifestyle. *Curr Opin Urol* 28:88–92. <https://doi.org/10.1097/MOU.0000000000000452>
- Witlox WJA, van Osch FHM, Brinkman M et al (2019) An inverse association between the Mediterranean diet and bladder cancer risk: a pooled analysis of 13 cohort studies. *Eur J Nutr*. <https://doi.org/10.1007/s00394-019-01907-8>
- Pelucchi C, Galeone C, Tramacere I et al (2012) Alcohol drinking and bladder cancer risk: a meta-analysis. *Ann Oncol Off J Eur Soc Med Oncol* 23:1586–1593. <https://doi.org/10.1093/annonc/mdr460>
- Botteri E, Ferrari P, Roswall N et al (2017) Alcohol consumption and risk of urothelial cell bladder cancer in the European prospective investigation into cancer and nutrition cohort. *Int J Cancer* 141:1963–1970. <https://doi.org/10.1002/ijc.30894>
- Zaitu M, Kawachi I, Takeuchi T, Kobayashi Y (2017) Alcohol consumption and risk of upper-tract urothelial cancer. *Cancer Epidemiol* 48:36–40. <https://doi.org/10.1016/j.canep.2017.03.002>
- Stroup DF, Berlin JA, Morton SC et al (2000) Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 283:2008–2012
- Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Available from: [http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.htm](http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm). Accessed 30 Oct 2017
- Cochrane Handbook for Systematic Reviews of Interventions. <http://handbook-5-1.cochrane.org/>. Accessed 19 Apr 2018
- Howe GR, Burch JD, Miller AB et al (1980) Tobacco use, occupation, coffee, various nutrients, and bladder cancer. *J Natl Cancer Inst* 64:701–713
- Cartwright RA, Adib R, Glashan R, Gray BK (1981) The epidemiology of bladder cancer in West Yorkshire. A preliminary report on non-occupational aetiologies. *Carcinogenesis* 2:343–347
- Najem GR, Louriya DB, Seebode JJ et al (1982) Life time occupation, smoking, caffeine, saccharine, hair dyes and bladder carcinogenesis. *Int J Epidemiol* 11:212–217
- Thomas DB, Uhl CN, Hartge P (1983) Bladder cancer and alcoholic beverage consumption. *Am J Epidemiol* 118:720–727
- Bravo MP, Del Rey CJ, Conde M (1987) Bladder cancer and the consumption of alcoholic beverages in Spain. *Eur J Epidemiol* 3:365–369

21. Mommsen S, Aagaard J, Sell A (1983) An epidemiological study of bladder cancer in a predominantly rural district. *Scand J Urol Nephrol* 17:307–312
22. Brownson RC, Chang JC, Davis JR (1987) Occupation, smoking, and alcohol in the epidemiology of bladder cancer. *Am J Public Health* 77:1298–1300
23. Risch HA, Burch JD, Miller AB et al (1988) Dietary factors and the incidence of cancer of the urinary bladder. *Am J Epidemiol* 127:1179–1191
24. Slattery ML, Schumacher MC, West DW, Robison LM (1988) Smoking and bladder cancer. The modifying effect of cigarettes on other factors. *Cancer* 61:402–408
25. Nomura A, Kolonel LN, Yoshizawa CN (1989) Smoking, alcohol, occupation, and hair dye use in cancer of the lower urinary tract. *Am J Epidemiol* 130:1159–1163
26. Mills PK, Beeson WL, Phillips RL, Fraser GE (1991) Bladder cancer in a low risk population: results from the Adventist Health Study. *Am J Epidemiol* 133:230–239
27. Kunze E, Chang-Claude J, Frentzel-Beyme R (1992) Life style and occupational risk factors for bladder cancer in Germany. A case-control study. *Cancer* 69:1776–1790
28. Chyou PH, Nomura AM, Stemmermann GN, Hankin JH (1993) A prospective study of alcohol, diet, and other lifestyle factors in relation to obstructive uropathy. *Prostate* 22:253–264
29. Momas I, Daurès JP, Festy B et al (1994) Relative importance of risk factors in bladder carcinogenesis: some new results about Mediterranean habits. *Cancer Causes Control CCC* 5:326–332
30. Nakata S, Sato J, Ohtake N et al (1995) Epidemiological study of risk factors for bladder cancer. *Hinyokika Kyo* 41:969–977
31. Bruemmer B, White E, Vaughan TL, Cheney CL (1997) Fluid intake and the incidence of bladder cancer among middle-aged men and women in a three-county area of western Washington. *Nutr Cancer* 29:163–168. <https://doi.org/10.1080/01635589709514619>
32. Donato F, Boffetta P, Fazioli R et al (1997) Bladder cancer, tobacco smoking, coffee and alcohol drinking in Brescia, northern Italy. *Eur J Epidemiol* 13:795–800
33. Pohlabeled H, Jöckel KH, Bolm-Audorff U (1999) Non-occupational risk factors for cancer of the lower urinary tract in Germany. *Eur J Epidemiol* 15:411–419
34. Lu CM, Lan SJ, Lee YH et al (1999) Tea consumption: fluid intake and bladder cancer risk in Southern Taiwan. *Urology* 54:823–828
35. Geoffroy-Perez B, Cordier S (2001) Fluid consumption and the risk of bladder cancer: results of a multicenter case-control study. *Int J Cancer* 93:880–887
36. Zeegers MP, Volovics A, Dorant E et al (2001) Alcohol consumption and bladder cancer risk: results from The Netherlands Cohort Study. *Am J Epidemiol* 153:38–41
37. Pelucchi C, Negri E, Franceschi S et al (2002) Alcohol drinking and bladder cancer. *J Clin Epidemiol* 55:637–641
38. Wakai K, Hirose K, Takezaki T et al (2004) Foods and beverages in relation to urothelial cancer: case-control study in Japan. *Int J Urol Off J Jpn Urol Assoc* 11:11–19
39. Djoussé L, Schatzkin A, Chibnik LB et al (2004) Alcohol consumption and the risk of bladder cancer in the Framingham Heart Study. *J Natl Cancer Inst* 96:1397–1400. <https://doi.org/10.1093/jnci/djh263>
40. Cao W, Cai L, Rao J-Y et al (2005) Tobacco smoking, GSTP1 polymorphism, and bladder carcinoma. *Cancer* 104:2400–2408. <https://doi.org/10.1002/ncr.21446>
41. Jiang X, Castela JE, Groshen S et al (2007) Alcohol consumption and risk of bladder cancer in Los Angeles County. *Int J Cancer* 121:839–845. <https://doi.org/10.1002/ijc.22743>
42. Demirel F, Cakan M, Yalçinkaya F et al (2008) The association between personal habits and bladder cancer in Turkey. *Int Urol Nephrol* 40:643–647. <https://doi.org/10.1007/s11255-008-9331-1>
43. Allen NE, Beral V, Casabonne D et al (2009) Moderate alcohol intake and cancer incidence in women. *J Natl Cancer Inst* 101:296–305. <https://doi.org/10.1093/jnci/djn514>
44. Benedetti A, Parent M-E, Siemiatycki J (2009) Lifetime consumption of alcoholic beverages and risk of 13 types of cancer in men: results from a case-control study in Montreal. *Cancer Detect Prev* 32:352–362
45. Zaitu M, Nakamura F, Toyokawa S et al (2016) Risk of alcohol consumption in bladder cancer: case-control study from a nationwide inpatient database in Japan. *Tohoku J Exp Med* 239:9–15. <https://doi.org/10.1620/tjem.239.9>
46. Masaoka H, Ito H, Soga N et al (2016) Aldehyde dehydrogenase 2 (ALDH2) and alcohol dehydrogenase 1B (ADH1B) polymorphisms exacerbate bladder cancer risk associated with alcohol drinking: gene-environment interaction. *Carcinogenesis* 37:583–588. <https://doi.org/10.1093/carcin/bgw033>
47. Masaoka H, Matsuo K, Sawada N et al (2017) Alcohol consumption and bladder cancer risk with or without the flushing response: the Japan Public Health Center-based Prospective Study. *Int J Cancer* 141:2480–2488. <https://doi.org/10.1002/ijc.31028>
48. Grant RL (2014) Converting an odds ratio to a range of plausible relative risks for better communication of research findings. *BMJ* 348:f7450. <https://doi.org/10.1136/bmj.f7450>
49. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. *BMJ* 315:629–634. <https://doi.org/10.1136/bmj.315.7109.629>
50. The Lancet null (2017) Alcohol and cancer. *Lancet Lond Engl* 390:2215. [https://doi.org/10.1016/S0140-6736\(17\)32868-4](https://doi.org/10.1016/S0140-6736(17)32868-4)
51. Secretan B, Straif K, Baan R et al (2009) A review of human carcinogens—Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. *Lancet Oncol* 10:1033–1034
52. Ohashi S, Miyamoto S, Kikuchi O et al (2015) Recent advances from basic and clinical studies of esophageal squamous cell carcinoma. *Gastroenterology* 149:1700–1715. <https://doi.org/10.1053/j.gastro.2015.08.054>
53. Emspak J (2016) Alcohol: fortifying spirits. *Nature* 537:S103–S104. <https://doi.org/10.1038/537S103a>
54. Ehdai B, Furberg H, Zabor EC et al (2013) Impact of smoking status at diagnosis on disease recurrence and death in upper tract urothelial carcinoma. *BJU Int* 111:589–595. <https://doi.org/10.1111/j.1464-410X.2012.11260.x>
55. Rink M, Furberg H, Zabor EC et al (2013) Impact of smoking and smoking cessation on oncologic outcomes in primary non-muscle-invasive bladder cancer. *Eur Urol* 63:724–732. <https://doi.org/10.1016/j.eururo.2012.08.025>
56. Soria F, Marra G, Čapoun O et al (2018) Prevention of bladder cancer incidence and recurrence: tobacco use. *Curr Opin Urol* 28:80–87. <https://doi.org/10.1097/MOU.0000000000000453>

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

## Affiliations

Mihai Dorin Vartolomei<sup>1,2</sup>  · Takehiro Iwata<sup>1,3</sup> · Beat Roth<sup>4</sup> · Shoji Kimura<sup>1,5</sup> · Romain Mathieu<sup>1,6</sup> · Matteo Ferro<sup>7</sup> · Shahrokh F. Shariat<sup>1,8,9,10,11</sup> · Christian Seitz<sup>1</sup>

<sup>1</sup> Department of Urology, Comprehensive Cancer Center, Vienna General Hospital, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria

<sup>2</sup> Department of Cell and Molecular Biology, University of Medicine, Pharmacy, Sciences and Technology, Targu Mures, Romania

<sup>3</sup> Department of Urology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

<sup>4</sup> Department of Urology, University of Bern, Bern, Switzerland

<sup>5</sup> Department of Urology, Jikei University School of Medicine, Tokyo, Japan

<sup>6</sup> Department of Urology, Rennes University Hospital, Rennes, France

<sup>7</sup> Division of Urology, European Institute of Oncology, Milan, Italy

<sup>8</sup> Department of Urology, Weill Cornell Medical College, New York, NY, USA

<sup>9</sup> Department of Urology, Second Faculty of Medicine, Charles University, Prague, Czech Republic

<sup>10</sup> Institute for Urology and Reproductive Health, I.M. Sechenov First Moscow State Medical University, Moscow, Russia

<sup>11</sup> Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX, USA