## UNIVERSITY<sup>OF</sup> BIRMINGHAM

### **Research at Birmingham**

# Total fluid intake and the risk of recurrence in patients with non-muscle invasive bladder cancer:

Jochems, Sylvia; Van Osch, Frits; Reulen, Raoul; van Hensbergen, Mitch ; Nekeman, Duncan; Pirrie, Sarah; Wesselius, Anke; van Schooten, Frederik J; James, Nicholas; Michael Wallace, A; Bryan, Richard; Cheng, Kar; Zeegers, Maurice

DOI: 10.3233/BLC-180172

License: None: All rights reserved

Document Version Peer reviewed version

Citation for published version (Harvard):

Jochems, S, Van Osch, F, Reulen, R, van Hensbergen, M, Nekeman, D, Pirrie, S, Wesselius, A, van Schooten, FJ, James, N, Michael Wallace, A, Bryan, R, Cheng, K & Zeegers, M 2018, 'Total fluid intake and the risk of recurrence in patients with non-muscle invasive bladder cancer: a prospective cohort study', Bladder Cancer, vol. 4, no. 3, pp. 303-310. https://doi.org/10.3233/BLC-180172

Link to publication on Research at Birmingham portal

#### Publisher Rights Statement:

Final Version of Record forthcoming in Bladder Cancer - http://www.bladdercancerjournal.com/

#### **General rights**

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

• Users may freely distribute the URL that is used to identify this publication.

• Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.

User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

#### Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

l	Total fluid intake and the risk of recurrence in patients with non-muscle invasive bladder

- 2 3 cancer: a prospective cohort study

4	Sylvia H.J. Jochems* (1, 2), Frits H.M. van Osch (1, 2), Raoul C. Reulen (3), Mitch van
5	Hensbergen (2), Duncan Nekeman (1), Sarah J. Pirrie (1), Anke Wesselius (2), Frederik J.
6	van Schooten (2), Nicholas D. James (1, 4), D. Michael A. Wallace (1, 4), Richard T. Bryan
7	(1), K.K. Cheng (3), Maurice P. Zeegers (1, 2)
8	
9	(1) Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham,
10	United Kingdom
11	(2) School for Nutrition and Translational Research in Metabolism, Maastricht
12	University, The Netherlands
13	(3) Institute of Applied Health Research, department of Public Health, Epidemiology and
14	Biostatistics, University of Birmingham, United Kingdom
15	(4) University Hospital Birmingham, NHS Foundation Trust, Birmingham, United
16	Kingdom
17	
18	*Corresponding author contact information: Sylvia H.J. Jochems, Maastricht University, Department
19	of Complex Genetics and Epidemiology, PO Box 616, 6200 MD Maastricht, the Netherlands
20	Email: s.jochems@maastrichtuniversity.nl
21	
22	Keywords: fluid intake, bladder cancer, recurrence
23	

#### 25 ABSTRACT

Objectives: To investigate the role of fluid intake from beverages before and after a 26 27 diagnosis of bladder cancer in relation to the risk of developing bladder cancer recurrence. Study design: Prospective cohort study. Methods: 716 patients with non-muscle invasive 28 29 bladder cancer (NMIBC), who received transurethral resection of a primary bladder tumour 30 (TURBT) and completed self-administrated questionnaires on usual fluid intake from 31 beverages at time of diagnosis (over the year before diagnosis) and during follow-up (over 32 the year after diagnosis), were included. Multivariable Cox regression was used to calculate 33 hazard ratios and 95% confidence intervals of developing recurrent bladder cancer in relation 34 to the intake of total fluid, total alcohol, and individual beverages. Results: During 2,025 35 person-years of follow-up, 238 (33%) of the included 716 NMIBC patients developed one or 36 more recurrences of bladder cancer. Total fluid intake before diagnosis was not associated 37 with a first recurrence of bladder cancer when comparing the highest and lowest intake group 38 (HR=0.98, 95% C.I. 0.70-1.38, p=0.91). Comparable results were obtained for total fluid 39 intake pre-diagnosis and the risk of developing multiple recurrences of bladder cancer 40 (HR=1.01, 95% C.I. 0.87-1.19, p=0.85). A total of 379 of the 716 patients reported on usual 41 fluid intake within 1 year of diagnosis. No significant associations between total fluid intake 42 1 year after diagnosis and a first recurrence of bladder cancer were found when comparing 43 the highest and lowest intake group (HR=0.91; 95% C.I. 0.60-1.37, p=0.65) or with multiple 44 recurrences of bladder cancer (HR=1.06; 95% C.I. 0.89-1.26, p=0.54). In addition, total 45 alcohol intake and individual beverages were not associated with bladder cancer recurrence. **Conclusions:** The results indicate that an individual's fluid intake from beverages is unlikely 46 47 to have an important role in bladder cancer recurrence.

48

#### 49 INTRODUCTION

Non-muscle-invasive bladder cancer (NMIBC) is the most common malignancy of the 50 51 urinary tract and has a high rate of recurrence despite adequate therapy. Identification of 52 modifiable risk factors could reduce the risk of developing recurrences and improve 53 prognosis. The urogenous contact theory hypothesizes that an increased voiding frequency 54 may reduce bladder cancer risk [1,2]. By increasing the intake of fluids, potential carcinogens 55 present in the urine are diluted and the voiding frequency stimulated. By reducing the contact 56 time of carcinogens with the bladder urothelium, the risk of bladder cancer decreases. On the 57 contrary, it has been suggested that when the bladder wall is extended from a high volume of 58 urine, carcinogens can come into contact with deeper layers of the bladder urothelium and increase bladder cancer risk [3]. In addition, in some parts of the world drinking water 59 60 contaminated with a high concentration of arsenic could increase the risk of bladder cancer 61 [4]. It is conceivable that the theories about fluid intake and the risk of developing bladder 62 cancer represent a modifiable factor of importance in bladder cancer prognosis as well [5–7]; 63 it would be a compelling strategy to simply increase or decrease fluid intake to decrease the 64 risk of recurrence. To our knowledge, only Donat et al. [8] investigated the impact of total 65 fluid intake on tumour recurrence in patients with NMIBC. At each visit, all patients undergoing surveillance for recurring tumours completed a self-administered fluid intake 66 67 questionnaire that measured total fluid intake during a 24-hour period. Results of this study 68 indicated that daily fluid intake levels did not affect recurrence and that the types of fluids 69 imbibed may be more important than the total amount [8]. Therefore, the present study 70 investigates the role of individual beverages, total alcohol and total fluid intake (over the year 71 before and the year after diagnosis) and the risk of developing one or more recurrences of 72 bladder cancer.

#### METHODS

#### The Bladder Cancer Prognosis Programme

This study is part of the Bladder Cancer Prognosis Programme (BCPP), a prospective cohort study in the West Midlands region of England. Details of the cohort have been published previously [9]. Briefly, during the enrolment period (December 2005 - October 2011), a total of 1,550 male and female patients (age  $\geq$ 18 years) were enrolled based on abnormal cystoscopic findings suggestive of bladder cancer. Transurethral resection of the primary bladder tumour (TURBT) was followed by cytoscopic surveillance. Optimal additional treatment comprised intravesical chemotherapy with mitomycin C within 24 hours of TURBT and/or a course of further mitomycin C or intravesical BCG, as per contemporary European Association of Urology guidelines. Bladder cancer recurrence was defined as the new occurrence of a non-muscle invasive bladder tumour and excluding recurrence identified at the first check cystoscopy. Written informed consent was obtained from all participants. The study protocol was approved by the Nottingham Research Ethics Committee (06/MRE04/65) and registered on ClinicalTrials.gov (NCT00553566).

#### Data collection

Around the time of diagnosis, just prior to, or just post TURBT,, data on medical history, socio-demographics, quality of life, and health-related lifestyle (including dietary intake) were collected by a trained research nurse using semi-structured face-to-face interviews and a questionnaire. The research nurse and patient went through the questionnaire page by page. Patients were asked about habitual dietary intake over the previous year. The developed version of the food-frequency questionnaire (FFQ) aims to assess the dietary intake, by asking the participants to report the frequency of consumption of approximately 16-line items

over the last year. More specifically, the frequency of fluid intake from beverages asked in the questionnaire consisted of six levels: never or less than once per month, one to three times per month, once a week, two to four times per week, five to six times per week, or at least once per day. For each drink, a measure size was provided (e.g. cup, (small) glass, pub measure (2.5cl), or (half) pint glass). The frequency of intake of each beverage was multiplied by their measure size to calculate the millilitres of fluids consumed per day. Total fluid intake was computed as the sum of servings of all beverages in the questionnaire: winechampagne, fortified wine, beer, cider, spirits, liqueurs, coffee, tea, hot chocolate, soup, ovaltine-horlicks, fizzy pop, pure fruit juice, fruit squash, milk, and water. Total alcohol intake included alcoholic beverages only: wine-champagne, fortified wine, beer, cider, spirits, and liqueurs. Repeated fluid intake from beverages was collected through a postal follow-up questionnaire one year after diagnosis.

#### Exclusion criteria

A total of 244 participants with no evidence of a bladder tumour (T0), patients who had a tumour that could not be assessed (Tx) (n=116), who had muscle invasive bladder cancer (MIBC) (n=275), who received no TURBT (n=16), who had radiotherapy (on suspicion of MIBC) (n=8), who had incomplete data on tumour characteristics (e.g. stage, grade, size, multiplicity) (n=53) and smoking (n=94), and had missing data on pre-diagnosis fluid intake (n=28), were all excluded from this study (Figure 1). The final analysis for fluid intake over the year before diagnosis comprised 716 patients. More than a third of these 716 patients did not complete a follow-up questionnaire one year after diagnosis (n=278) or developed a recurrence of bladder cancer before completing the follow-up questionnaire (n=59). Therefore, a total of 379 patients remained for investigating the association between fluid intake over the year after diagnosis and bladder cancer recurrence.

#### Statistical Analysis

According to the UK government recommendations on eating healthy and achieving a balanced diet, anybody living in a maritime climate should consume at least 1,200 mL of fluids from drinks a day [10]. Patients were divided into three groups: a group with an intake of 250mL – 850mL of total fluid per day, a group consuming 850mL – 1,200 mL of total fluid per day, or a group with a total intake of more than the recommended 1,200 mL of fluid per day. Patients became at risk for a recurrence of bladder cancer from the date of TURBT and remained at risk until the earliest occurrence of a recurrence, cystectomy, death, the most recent surveillance cystoscopy, or study end (five years post-TURBT). Cox regression was used to calculate hazard ratios (HRs) and 95% confidence intervals (95% C.I.) of developing a first recurrence of bladder cancer in relation to total fluid intake, total alcohol intake, and individual beverages. To identify possibly influential outliers in total fluid and alcohol intake, Cook's Distance was used. The association of fluid intake with recurrent bladder cancer was examined in both crude and multivariate models. Confounders were considered a priori based on known prognostic factors for NMIBC recurrence from the European Association of Urology guidelines and included: age at diagnosis (continuous) [11], sex (male/female) [12], smoking status (never/former/current smoker) [13], and tumour characteristics including stage (pTa/pT1/pTis), grade (1/2/3), size of largest tumour (diameter <3cm/≥3cm), and tumour multiplicity (1/>1) [14–16].

Conditional risk set modelling was applied to investigate time to each recurrent event and analysis time was reset at each event [17]. For this analysis, re-resection of tumours (yes/no) was added as a confounder. The proportional hazards assumption was checked in all models using Schoenfeld residuals [18]. Cumulative incidence functions (CIF) accounting for competing risks (death and cystectomy) were made [19]. These models are conditional as the failure times are conditional on the occurrence of the prior recurrence, i.e. a second

recurrence cannot occur before the first recurrence. P-values were 2-sided with a significance level of 0.05. All statistical analyses were performed using Stata software version 14.

#### RESULTS

#### Baseline characteristics and number of recurrences

During 2,025 person-years of follow-up (mean (SD) follow-up 3.7 (1.5) years), 238 (33%) of the 716 NMIBC patients developed one or more recurrences of bladder cancer. More specifically, 80 (34%) of these 238 patients developed a second recurrence, 35 (15%) a third recurrence, 17 (8%) a fourth recurrence, five (3%) a fifth recurrence, two (1%) a sixth recurrence, and one (1%) a seventh recurrence. Patient characteristics at diagnosis and initial treatment are presented in Table 1. The median age at diagnosis was 71 years and most patients were male (80%), Caucasian (97%), and current or former smokers (86%). The average intake of fluid was relatively evenly distributed between patients who had a recurrence of bladder cancer and those who had not (mean total fluid intake 1,087 mL per day and 1,103 mL per day, respectively).

#### Total fluid intake and bladder cancer recurrence

Table 2 presents HRs with corresponding 95% C.I. for total fluid intake over the year before diagnosis from beverages and time to a first bladder cancer recurrence and multiple bladder cancer recurrences among 716 NMIBC patients. Total fluid intake the year before diagnosis did not affect the recurrence of a first bladder tumour (HR= 0.98, 95% C.I. 0.70-1.38, p=0.91) when adjusted for age, sex, smoking status, stage, grade, and tumour size and multiplicity. The association between total fluid intake the year before diagnosis and time to multiple recurrences showed similar results (HR= 1.01, 95% C.I. 0.87-1.19, p=0.85) when adjusted for the same confounders and tumour re-resection (second transurethral resection).

Table 3 presents the results for the remaining 379 NMIBC patients on total fluid intake after diagnosis – no significant associations were observed between total fluid intake and the development of a first bladder cancer recurrence (HR=0.91; 95% C.I. 0.60-1.37, p=0.65) or

multiple recurrences (HR=1.06; 95% C.I. 0.89-1.26, p=0.54) when corrected for known prognostic factors for NMIBC recurrence provided in the European Association of Urology guidelines (including age, sex, smoking status, tumour characteristics and tumour re-resection).

#### Total alcohol and individual beverages intake and bladder cancer recurrence

Results of the Cox proportional hazard models predicting the development of recurrence based on total alcohol intake and individual beverages can be found in the online supplementary file (Table S1-S8). Among 716 NMIBC patients, total alcohol intake before diagnosis (highest intakes >125mL versus lowest intakes 0mL) was not associated with a first bladder tumour (HR= 0.97; 95% CI 0.70-1.36) in the most extensive model (adjusted for age, sex, smoking status, stage, grade, and tumour size and multiplicity) (Table S1). Similar results were found for total alcohol intake prior to a diagnosis of bladder cancer and multiple recurrences of bladder cancer (HR= 0.97; 95% CI 0.84-1.11) when corrected for the same confounders as in the time to a first recurrence analysis plus re-resection of a bladder tumour (Table S2).

None of the individual alcoholic beverages including beer, cider, wine/champagne, fortified wine, spirits or liqueurs consumed prior to bladder cancer diagnosis influenced the risk of developing a first or multiple recurrences of bladder cancer when comparing the highest frequency of intake 'at least 1 per day' versus the lowest frequency of intake /never/less than 1 per month' (Table S1-S2). The warm beverages coffee, tea, hot chocolate, ovaltine/horlicks and soup were also investigated. No associations were found when comparing the frequencies of these warm beverages (at least one per day versus never/less than 1 per month before diagnosis) and a first or multiple recurrences of bladder cancer (Table S3-S4). In addition, pre-diagnosis consumption of the cold beverages milk, water, fizzy pop, pure fruit juice, and

fruit squash/cordial, did not affect the development of one or multiple recurrences of bladder cancer when comparing the highest versus the lowest frequency intakes.

Among the 379 NMIBC that remained for analyses one year after a diagnosis of bladder cancer, total alcohol intake was not associated with a first recurrence (HR= 1,01; 95% CI 0.65-1.58) or multiple recurrences (HR= 1,05; 95% CI 0.88-1.25) (Table S5-S6). Consumption of alcoholic beverages one year after a diagnosis of bladder cancer was not related to the development of bladder cancer recurrences (Table S5-S6). Finally, no associations were found for usual warm and hot non-alcoholic beverages consumption and one or more recurrence of bladder cancer (Table S7-S8).

#### DISCUSSION

The results of this study indicate that there is no evidence of an association between total fluid, total alcohol, or individual beverages (before and after diagnosis) and recurrence of a bladder tumour in patients diagnosed for NMIBC. These results are consistent with the findings of Donat *et al.* [8] who also concluded it remains unclear whether increased total fluid intake is beneficial against the development of bladder cancer recurrence. With regard to fluid intake and the risk of developing bladder cancer for the first time, the results of a recent case-control study have shown that there was no association with total water intake from both beverages and foods [20]. Also the results of a meta-analysis demonstrated no association between total fluid intake and the risk of developing primary bladder cancer [21]. However, subgroup analyses indicated that high fluid intake could increase the risk of bladder cancer in European men (and possibly American men) and decrease the risk of bladder cancer in Asian men [21].

It seems plausible, however, that substances in beverages could be involved in carcinogenesis in the bladder as they come into contact with the bladder urothelium when excreted via the urine. The numerous substances may react differently with cells of the bladder urothelium and be involved in several different pathways associated with cancer pathogenesis including inflammation, cell survival and self-renewal of cancer stem cells [22,23]. A possible explanation for the lack of an association between fluid intake from beverages and bladder cancer recurrence could be that tumour recurrence is more influenced by tumour biology, field cancerization, and cancer treatment than continued exposure of potential carcinogens with the bladder urothelium [24–26]. Incomplete resection of the primary tumour and tumour cell re-implantation remain to be the most influential factors in the development of NMIBC recurrence [26]. Finally, it is inevitable that fluid intake was not measured without error -

recall bias and measurement errors in dietary intake cannot be excluded and are a common limitation of epidemiological studies.

#### CONCLUSIONS

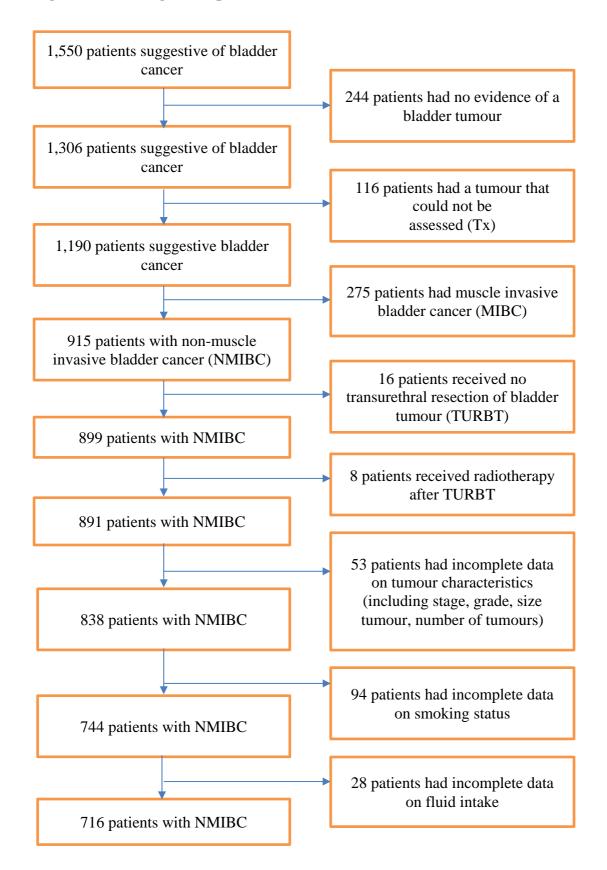
The results of this study indicate that fluid intake from beverages is unlikely to have a dominant role in influencing the risk of subsequent recurrence(s). Proposed strategies aimed at decreasing contact time of carcinogens with the urothelium by increasing fluid intake are unlikely to delay or prevent the development of bladder cancer recurrence in NMIBC patients.

#### **Conflict of Interest statement**

All authors certify that they have no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

#### Funding

BCPP was supported by Cancer Research UK, the Institute of Applied Health Research (IAHR), and the Institute of Cancer and Genomic Sciences of the University of Birmingham.



#### Figure 1. Flow diagram of patients selection, with exclusion criteria

#### **Table legends:**

Table 1. Patient characteristics at diagnosis for 716 NMIBC patients treated with transurethral resection of a primary bladder tumour

Table 2. Hazard ratios (HR) and 95% confidence intervals (95% C.I.) for Cox proportional hazard models predicting a first and multiple recurrences of bladder cancer, based on total fluid consumed in the year before diagnosis, in 716 NMIBC patients

Table 3. Hazard ratios (HR) and 95% confidence intervals (95% C.I.) for Cox proportional hazard models predicting a first and multiple recurrences of bladder cancer, based on total fluid consumed in the year after diagnosis, in 379 NMIBC patients

Online Supplemental Tables S1-S8. Hazard ratios (HR) and 95% confidence intervals (95% C.I.) for Cox proportional hazard models predicting a first and multiple recurrences of bladder cancer, based on alcohol intake from beverages and individual beverages consumed in the year before and in the year after diagnosis

		Number (%)	
Age at time of diagnosis (years)		· ·	
median (25th-75th percentile)	71 (63-77)		
Sex	Male	573 (80%)	
	Female	143 (20%)	
Smoking status	Current smokers	335 (47%)	
-	Former smokers	281 (39%)	
	Never smokers	100 (14%)	
Alcohol consumption	Drinkers	540 (75%)	
-	Non-drinkers	176 (25%)	
Educational level	High	89 (12%)	
	Middle	91 (13%)	
	None/Low	163 (23%)	
BCG intravesical immunotherapy	Yes	111 (15%)	
15	No	275 (39%)	
Mitomycin C intravesical chemotherapy	Yes	337 (47%)	
, , , , , , , , , , , , , , , , , , , ,	No	73 (10%)	
Tumour stage	рТа	478 (67%)	
J	pT1	232 (32%)	
	pTis	6 (1%)	
Tumour grade	1	206 (29%)	
-	2	261 (36%)	
	3	249 (35%)	
Size largest tumour (cm)	<3	449 (63%)	
-	≥3	267 (37%)	
Tumours multiplicity	1	427 (59%)	
	>1	289 (41%)	
No of recurrences over 5 years	0	478 (67%)	
2	1	158 (22%)	
	>1	80 (11%)	

#### Table 1. Patient characteristics at diagnosis for 716 NMIBC patients treated with transurethral resection of a primary bladder tumour

Where the data contains missing values the percentages do not add up to 100%

Table 2. Hazard ratios (HR) a				proportional	hazard models predicting	a first and mu	Itiple recurrences of bladd	er cancer, bas	sed on total					
luid intake over the year before diagnosis, in 716 NMIBC patients														
	Model 1* Model 2** Model 3***													
	n	events	HR (95% C.I.)	p-value	HR (95% C.I.)	p-value	HR (95% C.I.)	p-value	p for trend					
Time to first recurrence														
250-850 mL	205	64	ref		ref		ref		0.86					
850 – 1200 mL	257	98	1.24 (0.90-1.69)	0.19	1.26 (0.92-1.72)	0.16	1.17 (0.85-1.62)	0.33						
>1200 mL	254	76	0.92 (0.66-1.28)	0.62	0.93 (0.67-1.31	0.70	0.98 (0.70-1.38)	0.91						

250-850 mL 205 92 ref 0.78 ref ref 850 – 1200 mL 0.95 (0.83-1.09) 0.95 (0.83-1.08) 257 171 0.48 0.96 (0.84-1.10) 0.57 0.42 >1200 mL 254 115 1.05 (0.90-1.22) 0.51 1.05 (0.90-1.23) 0.54 1.01 (0.87-1.19) 0.85 \*Model 1 is unadjusted, \*\*Model 2 is adjusted for age, sex, and smoking status, \*\*\*Model 3 is adjusted for age, sex, smoking status, tumour stage, grade, size and

Time to multiple recurrences

\*Model 1 is unadjusted, \*\*Model 2 is adjusted for age, sex, and smoking status, \*\*\*Model 3 is adjusted for age, sex, smoking status, tumour stage, grade, size and multiplicity. In the time to multiple recurrences analyses, Model 2 and Model 3 were additionally adjusted for the variable re-resection of a bladder tumour (second transurethral resection)

Table 3. Hazard ratios (HR) and the year after diagnosis, in 379				·	1 5	•			
			Model 1*		Model 2**		Model 3***		
	n	events	HR (95% C.I.)	p-value	HR (95% C.I.)	p-value	HR (95% C.I.)	p-value	p for trend
Time to first recurrence									
250-850 mL	116	45	ref		ref		ref		0.65
850 – 1200 mL	124	48	1.08 (0.72-1.63)	0.71	1.04 (0.69-1.57)	0.86	1.07 (0.71-1.61)	0.76	
>1200 mL	139	46	0.81 (0.54-1.21)	0.31	0.80 (0.53-1.20)	0.27	0.91 (0.60-1.37)	0.65	
Time to multiple recurrences									
250-850 mL	116	67	ref		ref		ref		0.53
850 – 1200 mL	124	71	1.07 (0.91-1.25)	0.41	1.06 (0.91-1.24)	0.43	1.08 (0.91-1.27)	0.38	
>1200 mL	139	68	1.05 (0.87-1.26)	0.63	1.04 (0.86-1.26)	0.67	1.06 (0.89-1.26)	0.54	

\*Model 1 is unadjusted, \*\*Model 2 is adjusted for age, sex, and smoking status, \*\*\*Model 3 is adjusted for age, sex, smoking status, tumour stage, grade, size and multiplicity. In the time to multiple recurrences analyses, Model 2 and Model 3 were additionally adjusted for the variable re-resection of a bladder tumour (second transurethral resection)

#### REFERENCES

- [1] Silverman DT, Hartge P, Morrison AS, Devesa SS. Epidemiology of bladder cancer. Hematol Oncol Clin North Am 1992;6:1–30.
- [2] McDONALD DF, LUND RR. The role of the urine in vesical neoplasm. I. Experimental confirmation of the urogenous theory of pathogenesis. J Urol 1954;71:560–70.
- [3] Claude J, Kunze E, Frentzel-Beyme R, Paczkowski K, Schneider J, Schubert H. Life-style and occupational risk factors in cancer of the lower urinary tract. Am J Epidemiol 1986;124:578–89.
- [4] World Cancer Research Fund International/American Institute for Cancer Research. Continuous Update Project Report: Diet, Nutrition,
   Physical Activity and Bladder Cancer. 2015. n.d.
- [5] Michaud DS, Spiegelman D, Clinton SK, Rimm EB, Curhan GC, Willett WC, et al. Fluid intake and the risk of bladder cancer in men. N
   Engl J Med 1999;340:1390–7. doi:10.1056/NEJM199905063401803.
- [6] Zhou J, Smith S, Giovannucci E, Michaud DS. Reexamination of total fluid intake and bladder cancer in the health professionals followup study cohort. Am J Epidemiol 2012;175:696–705. doi:10.1093/aje/kwr359.
- [7] Pekmezi DW, Demark-Wahnefried W. Updated evidence in support of diet and exercise interventions in cancer survivors. Acta Oncol 2011;50:167–78. doi:10.3109/0284186X.2010.529822.
- [8] Donat SM, Bayuga S, Herr HW, Berwick M. Fluid intake and the risk of tumor recurrence in patients with superficial bladder cancer. J

Urol 2003;170:1777-80. doi:10.1097/01.ju.0000091803.35049.da.

- [9] Zeegers MP, Bryan RT, Langford C, Billingham L, Murray P, Deshmukh NS, et al. The West Midlands Bladder cancer prognosis programme: Rationale and design. BJU Int 2010;105:784–8. doi:10.1111/j.1464-410X.2009.08849.x.
- [10] Public Health England in association with the Welsh government, Food Standards Scotland and the Food Standards Agency in Northern Ireland. The Eatwell Guide. n.d.
- [11] Taylor JA, Kuchel GA. Bladder cancer in the elderly: clinical outcomes, basic mechanisms, and future research direction. Nat Clin Pract Urol 2009;6:135–44. doi:10.1038/ncpuro1315.
- [12] Fajkovic H, Halpern JA, Cha EK, Bahadori A, Chromecki TF, Karakiewicz PI, et al. Impact of gender on bladder cancer incidence, staging, and prognosis. World J Urol 2011;29:457–63. doi:10.1007/s00345-011-0709-9.
- [13] Wyszynski A, Tanyos SA, Rees JR, Marsit CJ, Kelsey KT, Schned AR, et al. Body mass and smoking are modifiable risk factors for recurrent bladder cancer. Cancer 2014;120:408–14. doi:10.1002/cncr.28394.
- [14] Stein JP, Grossfeld GD, Ginsberg DA, Esrig D, Freeman JA, Figueroa AJ, et al. Prognostic markers in bladder cancer: a contemporary review of the literature. J Urol 1998;160:645–59.
- [15] Yan Y, Andriole GL, Humphrey PA, Kibel AS. Patterns of multiple recurrences of superficial (Ta/T1) transitional cell carcinoma of bladder and effects of clinicopathologic and biochemical factors. Cancer 2002;95:1239–46. doi:10.1002/cncr.10822.

- [16] Ather MH, Nazim SM. New and contemporary markers of prognosis in nonmuscle invasive urothelial cancer. Korean J Urol 2015;56:553.
   doi:10.4111/kju.2015.56.8.553.
- [17] Amorim LDAF, Cai J. Modelling recurrent events: A tutorial for analysis in epidemiology. Int J Epidemiol 2015;44:324–33.
   doi:10.1093/ije/dyu222.
- [18] D. Schoenfeld. Partial Residuals for The Proportionnal Hazards Regression Model. Biometrika 1982;69:239–41.
- [19] Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med 1999;18:695–706.
- [20] Di Maso M, Bosetti C, Taborelli M, Montella M, Libra M, Zucchetto A, et al. Dietary water intake and bladder cancer risk: An Italian case–control study. Cancer Epidemiol 2016;45:151–6. doi:10.1016/j.canep.2016.09.015.
- [21] Liu Q, Liao B, Tian Y, Chen Y, Luo D, Lin Y, et al. Total fluid consumption and risk of bladder cancer: a meta-analysis with updated data. Oncotarget 2017;8:55467–77. doi:10.18632/oncotarget.18100.
- [22] Prasad S, Phromnoi K, Yadav V, Chaturvedi M, Aggarwal B. Targeting Inflammatory Pathways by Flavonoids for Prevention and Treatment of Cancer. Planta Med 2010;76:1044–63. doi:10.1055/s-0030-1250111.
- [23] Kim YS, Farrar W, Colburn NH, Milner JA. Cancer stem cells: potential target for bioactive food components. J Nutr Biochem 2012;23:691–8. doi:10.1016/j.jnutbio.2012.03.002.

- [24] Takahashi T, Habuchi T, Kakehi Y, Mitsumori K, Akao T, Terachi T, et al. Clonal and chronological genetic analysis of multifocal cancers of the bladder and upper urinary tract. Cancer Res 1998;58:5835–41.
- [25] Simon R, Eltze E, Schäfer KL, Bürger H, Semjonow A, Hertle L, et al. Cytogenetic analysis of multifocal bladder cancer supports a monoclonal origin and intraepithelial spread of tumor cells. Cancer Res 2001;61:355–62.
- [26] Bryan RT, Collins SI, Daykin MC, Zeegers MP, Cheng K, Wallace DMA, et al. Mechanisms of recurrence of Ta/T1 bladder cancer. Ann R Coll Surg Engl 2010;92:519–24. doi:10.1308/003588410X12664192076935.

#### SUPPLEMENTARY DATA 'Total fluid intake and the risk of recurrence in patients with non-muscle invasive bladder cancer: a prospective cohort study'

Pre-diagnosis analysis

			Model 1*		Model 2**		Model 3***		
	n	events	HR (95% C.I.)	p-value	HR (95% C.I.)	p-value	HR (95% C.I.)	p-value	p trend
Total alcohol*								-	0.93
T1 (0 mL/day)	176	60	ref		ref		ref		
T2 (25 mL-125 mL/day)	231	75	0.91 (0.65-1.28)	0.60	0.94 (0.67-1.32)	0.72	0.90 (0.63-1.27)	0.55	
T3 (>125 mL/day)	306	102	0.95 (0.69-1.30)	0.74	1.00 (0.72-1.40)	0.98	0.97 (0.70-1.36)	0.87	
Beer (e.g. beer, lager, stout)			X /		· · · ·				
Never/less than 1 per month	316	108	ref		ref		ref		0.56
1-3 per month	92	26	0.77 (0.50-1.18)	0.23	0.83 (0.53-1.28)	0.40	0.81 (0.52-1.27)	0.36	
1 per week	68	31	1.38 (0.91-2.08)	0.13	1.46 (0.95-2.24)	0.08	1.41 (0.92-2.15)	0.11	
2-4 per week	141	42	0.82 (0.58-1.17)	0.27	0.87 (0.61-1.25)	0.46	0.88 (0.61-1.27)	0.50	
5-6 per week	44	14	0.89 (0.52-1.51)	0.66	0.95 (0.55-1.63)	0.84	0.78 (0.45-1.35)	0.37	
At least 1 per day	55	16	0.85 (0.50-1.45)	0.55	0.90 (0.52-1.55)	0.69	0.93 (0.54-1.58)	0.78	
Cider									
Never/less than 1 per month	667	215	ref		ref		ref		0.26
1-3 per month	28	14	2.11 (1.26-3.54)	0.00	2.29 (1.40-3.76)	0.00	1.96 (1.15-3.37)	0.01	
1 per week	11	5	1.36 (0.58-3.17)	0.48	1.31 (0.58-2.98)	0.51	1.17 (0.57-2.38)	0.67	
2-4 per week	5	2	1.66 (0.32-8.62)	0.54	2.07 (0.40-10.81)	0.39	2.38 (0.49-11.51)	0.28	
5-6 per week	1	0	-		-		-		
At least 1 per day	4	1	0.65 (0.09-4.65)	0.67	0.68 (0.10-4.81)	0.70	0.90 (0.16-5.25)	0.91	
Wine or champagne									
Never/less than 1 per month	412	133	ref		ref		ref		0.32
1-3 per month	74	21	0.84 (0.54-1.32)	0.45	0.87 (0.56-1.37)	0.55	0.84 (0.53-1.34)	0.47	
1 per week	55	20	1.19 (0.71-1.98)	0.52	1.25 (0.74-2.11)	0.41	1.38 (0.82-2.30)	0.22	
2-4 per week	89	29	0.92 (0.62-1.38)	0.69	0.95 (0.63-1.41)	0.78	0.98 (0.65-1.46)	0.91	
5-6 per week	36	14	1.25 (0.71-2.21)	0.43	1.25 (0.72-2.17)	0.43	1.21 (0.69-2.11)	0.50	
At least 1 per day	50	20	1.19 (0.75-1.88)	0.46	1.18 (0.75-1.86)	0.47	1.25 (0.78-2.01)	0.36	1

\*Q1 includes non-drinkers only, Q2 includes drinkers whose consumption corresponds with up to 1 large glass of wine or half a pint of beer/lager per day, Q3 includes drinkers whose consumption corresponds with more than 1 large glass of wine or half a pint of beer/cider per day. \*Model 1 was unadjusted, \*\*Model 2 was adjusted for age, sex, and smoking status, \*\*\*Model 3 was adjusted for age, sex, smoking status, and tumour stage, grade, size and multiplicity.

Table S1. (continued)									
			Model 1*		Model 2**		Model 3***		
	n	events	HR (95% C.I.)	p-value	HR (95% C.I.)	p-value	HR (95% C.I.)	p-value	p trend
Fortified wine (e.g. port, sherry, cinzano)									
Never/less than 1 per month	625	208	ref		ref		ref		0.54
1-3 per month	49	13	0.70 (0.41-1.22)	0.21	0.70 (0.41-1.19)	0.19	0.70 (0.41-1.18)	0.18	
1 per week	20	6	0.80 (0.37-1.76)	0.59	0.73 (0.33-1.60)	0.43	0.81 (0.38-1.74)	0.59	
2-4 per week	12	5	1.27 (0.55-2.94)	0.58	1.31 (0.59-2.92)	0.50	1.52 (0.66-3.50)	0.32	
5-6 per week	6	3	1.85 (0.60-5.74)	0.29	1.70 (0.60-4.81)	0.32	1.40 (0.51-3.84)	0.51	
At least 1 per day	4	2	1.99 (0.34-11.59)	0.44	2.09 (0.36-12.19)	0.41	2.49 (0.45-13.72)	0.29	
Spirits (e.g. gin, brandy, rum, vodka, whiskey)									
Never/less than 1 per month	455	140	ref		ref		ref		0.88
1-3 per month	91	38	1.34 (0.93-1.93)	0.12	1.42 (0.98-2.05)	0.06	1.42 (0.98-2.06)	0.06	
1 per week	53	23	1.50 (0.98-2.30)	0.06	1.50 (0.99-2.29)	0.06	1.58 (1.03-2.43)	0.04	
2-4 per week	66	21	1.00 (0.64-1.58)	1.00	1.03 (0.65-1.62)	0.91	1.08 (0.68-1.72)	0.74	
5-6 per week	15	5	1.11 (0.46-2.69)	0.81	1.06 (0.44-2.55)	0.90	1.01 (0.40-2.60)	0.98	
At least 1 per day	36	10	0.86 (0.46-1.63)	0.65	0.83 (0.44-1.56)	0.57	0.80 (0.43-1.48)	0.47	
Liqueurs (e.g. tia maria, baileys, cointreau)									
Never/less than 1 per month	671	220	ref		ref		ref		0.05
1-3 per month	31	9	0.83 (0.43-1.63)	0.59	0.83 (0.43-1.62)	0.59	0.77 (0.39-1.52)	0.45	
1 per week	6	2	0.93 (0.22-3.91)	0.92	0.89 (0.21-3.68)	0.87	0.85 (0.21-3.43)	0.81	
2-4 per week	5	3	2.45 (0.67-9.02)	0.18	2.16 (0.58-8.09)	0.25	1.73 (0.46-6.46)	0.42	
5-6 per week	0	0	-		-		-		
At least 1 per day	3	3	4.76 (2.63-8.62)	0.00	4.72 (2.75-8.11)	0.00	6.66 (4.56-9.74)	0.00	

			Model 1*		Model 2**		Model 3***		
	n	events	HR (95% C.I.)	p-value	HR (95% C.I.)	p-value	HR (95% C.I.)	p-value	p trend
Total alcohol*									
T1 (0 mL/day)	176	145	ref		ref		ref		0.87
T2 (25 mL-125 mL/day)	231	204	0.89 (0.77-1.02)	0.10	0.89 (0.77-1.03)	0.11	0.88 (0.77-1.02)	0.08	
T3 (>125 mL/day)	306	265	0.98 (0.87-1.11)	0.75	0.99 (0.86-1.13)	0.83	0.97 (0.84-1.11)	0.66	
Beer (e.g. beer, lager, stout)									
Never/less than 1 per month	316	166	ref		ref		ref		0.52
1-3 per month	92	38	0.97 (0.79-1.19)	0.76	0.98 (0.79-1.21)	0.83	0.96 (0.78-1.19)	0.73	
1 per week	68	63	1.03 (0.88-1.22)	0.69	1.04 (0.87-1.25)	0.65	1.05 (0.88-1.24)	0.61	
2-4 per week	141	58	1.08 (0.94-1.24)	0.28	1.09 (0.93-1.28)	0.27	1.08 (0.93-1.26)	0.31	
5-6 per week	44	27	0.97 (0.79-1.20)	0.80	0.99 (0.78-1.24)	0.90	0.88 (0.69-1.14)	0.33	
At least 1 per day	55	32	1.12 (0.92-1.35)	0.26	1.11 (0.90-1.37)	0.32	1.09 (0.88-1.37)	0.42	
Cider									
Never/less than 1 per month	667	348	ref		ref		ref		0.25
1-3 per month	28	22	1.04 (0.85-1.26)	0.70	1.03 (0.85-1.25)	0.76	1.00 (0.82-1.23)	0.98	
1 per week	11	10	0.88 (0.63-1.22)	0.44	0.87 (0.65-1.17)	0.37	0.87 (0.68-1.12)	0.29	
2-4 per week	5	3	3.27 (1.61-6.63)	0.00	3.34 (1.72-6.48)	0.00	3.64 (1.90-6.97)	0.00	
5-6 per week	1	0	-		-		-		
At least 1 per day	4	1	2.45 (2.02-2.98)	0.00	2.56 (2.11-3.12)	0.00	2.76 (2.19-3.46)	0.00	
Wine or champagne									
Never/less than 1 per month	412	210	ref		ref		ref		0.91
1-3 per month	74	33	1.15 (0.91-1.45)	0.25	1.15 (0.91-1.46)	0.24	1.18 (0.94-1.48)	0.17	
1 per week	55	26	1.35 (1.03-1.76)	0.03	1.35 (1.04-1.75)	0.03	1.29 (0.97-1.71)	0.08	
2-4 per week	89	49	1.03 (0.88-1.22)	0.69	1.03 (0.87-1.21)	0.75	1.01 (0.86-1.18)	0.90	
5-6 per week	36	33	0.84 (0.67-1.06)	0.14	0.86 (0.69-1.08)	0.19	0.89 (0.71-1.12)	0.33	
At least 1 per day	50	33	1.03 (0.87-1.23)	0.74	1.02 (0.86-1.21)	0.83	1.03 (0.86-1.22)	0.78	

\*Q1 includes non-drinkers only, Q2 includes drinkers whose consumption corresponds with up to 1 large glass of wine or half a pint of beer/lager per day, Q3 includes drinkers whose consumption corresponds with up to 1 large glass of wine or half a pint of beer/lager per day, Q3 includes drinkers whose consumption corresponds with more than 1 large glass of wine or half a pint of beer/cider per day. \*Model 1 was unadjusted, \*\*Model 2 was adjusted for age, sex, and smoking status, \*\*\*Model 3 was adjusted for age, sex, smoking status, and tumour stage, grade, size and multiplicity, and re-resection of a bladder tumour (second transurethral resection).

Table S2. (continued)									
			Model 1*		Model 2**		Model 3***		
	n	events	HR (95% C.I.)	p-value	HR (95% C.I.)	p-value	HR (95% C.I.)	p-value	p trend
Fortified wine (e.g. port, sherry, cinzano)									
Never/less than 1 per month	625	334	ref		ref		ref		0.48
1-3 per month	49	20	1.05 (0.81-1.37)	0.71	1.06 (0.82-1.37)	0.67	1.06 (0.83-1.35)	0.64	
1 per week	20	11	0.85 (0.56-1.30)	0.45	0.87 (0.57-1.34)	0.53	0.88 (0.58-1.35)	0.56	
2-4 per week	12	11	0.85 (0.65-1.12)	0.25	0.83 (0.65-1.06)	0.13	0.83 (0.70-0.99)	0.04	
5-6 per week	6	6	0.92 (0.78-1.08)	0.30	0.91 (0.77-1.08)	0.29	0.93 (0.73-1.18)	0.55	
At least 1 per day	4	2	1.54 (0.93-2.54)	0.09	1.54 (0.98-2.44)	0.06	1.52 (0.90-2.58)	0.12	
Spirits (e.g. gin, brandy, rum, vodka, whiskey)									
Never/less than 1 per month	455	218	ref		ref		ref		0.45
1-3 per month	91	73	0.94 (0.81-1.09)	0.40	0.93 (0.79-1.08)	0.34	0.91 (0.78-1.06)	0.23	
1 per week	53	42	0.97 (0.82-1.15)	0.75	0.97 (0.82-1.15)	0.70	1.00 (0.84-1.18)	0.96	
2-4 per week	66	28	1.00 (0.80-1.25)	0.99	1.01 (0.80-1.26)	0.96	0.98 (0.76-1.25)	0.84	
5-6 per week	15	8	1.17 (0.88-1.55)	0.29	1.19 (0.89-1.59)	0.25	1.25 (0.99-1.58)	0.06	
At least 1 per day	36	15	1.18 (0.87-1.60)	0.28	1.17 (0.87-1.58)	0.31	1.18 (0.87-1.59)	0.29	
Liqueurs (e.g. tia maria, baileys, cointreau)									
Never/less than 1 per month	671	355	ref		ref		ref		0.67
1-3 per month	31	13	1.08 (0.78-1.49)	0.65	1.07 (0.77-1.50)	0.68	0.96 (0.64-1.42)	0.82	
1 per week	6	7	0.89 (0.61-1.29)	0.53	0.88 (0.59-1.30)	0.51	0.82 (0.56-1.22)	0.34	
2-4 per week	5	5	1.18 (0.75-1.85)	0.47	1.21 (0.74-1.99)	0.44	1.22 (0.74-2.00)	0.44	
5-6 per week	0	0	-		-		-		
At least 1 per day	3	4	0.82 (0.60-1.11)	0.19	0.80 (0.57-1.12)	0.19	0.89 (0.64-1.23)	0.47	

			Model 1*		Model 2**		Model 3***		
	n	events	HR (95% C.I.)	p-value	HR (95% CI)	p-value	HR (95% C.I.)	p-value	p trend
Coffee			· · ·	•		•		-	
Never/less than 1 per month	152	39	ref		ref		ref		0.16
1-3 per month	39	15	1.60 (0.88-2.91)	0.12	1.79 (0.99-3.22)	0.05	1.84 (1.00-3.38)	0.05	
1 per week	46	14	1.13 (0.63-2.04)	0.68	1.19 (0.65-2.17)	0.58	1.03 (0.54-1.96)	0.94	
2-4 per week	78	27	1.35 (0.83-2.22)	0.23	1.36 (0.83-2.24)	0.22	1.34 (0.81-2.21)	0.26	
5-6 per week	34	13	1.43 (0.75-2.70)	0.27	1.58 (0.83-3.00)	0.16	1.46 (0.77-2.75)	0.25	
At least 1 per day	367	129	1.32 (0.92-1.88)	0.13	1.36 (0.94-1.96)	0.10	1.37 (0.94-2.00)	0.10	
Теа			· · · · ·						
Never/less than 1 per month	73	21	ref		ref		ref		0.54
1-3 per month	11	4	1.60 (0.54-4.72)	0.39	1.58 (0.53-4.66)	0.41	1.34 (0.43-4.14)	0.61	
1 per week	1	0	-		-		-		
2-4 per week	13	7	2.17 (0.99-4.77)	0.05	2.13 (0.96-4.74)	0.06	2.10 (0.92-4.76)	0.08	
5-6 per week	24	11	1.83 (0.91-3.70)	0.09	1.81 (0.89-3.67)	0.10	1.58 (0.78-3.20)	0.20	
At least 1 per day	594	194	1.23 (0.81-1.87)	0.32	1.18 (0.77-1.79)	0.45	1.21 (0.80-1.83)	0.37	
Hot chocolate									
Never/less than 1 per month	548	179	ref		ref		ref		0.73
1-3 per month	70	24	1.16 (0.76-1.77)	0.50	1.19 (0.78-1.81)	0.42	1.05 (0.68-1.61)	0.84	
1 per week	26	7	0.74 (0.36-1.52)	0.42	0.75 (0.37-1.54)	0.44	0.74 (0.35-1.58)	0.44	
2-4 per week	29	13	1.43 (0.83-2.46)	0.20	1.39 (0.82-2.38)	0.23	1.16 (0.68-2.00)	0.58	
5-6 per week	4	0	-		-		-		
At least 1 per day	39	14	1.22 (0.68-2.17)	0.50	1.15 (0.64-2.07)	0.64	1.26 (0.70-2.25)	0.44	
Ovaltine / Horlicks									
Never/less than 1 per month	634	212	ref		ref		ref		0.51
1-3 per month	21	5	0.61 (0.26-1.39)	0.24	0.61 (0.27-1.39)	0.24	0.61 (0.26-1.47)	0.27	
1 per week	12	4	1.10 (0.38-3.22)	0.86	1.09 (0.38-3.11)	0.87	1.02 (0.35-2.95)	0.97	
2-4 per week	16	7	1.38 (0.66-2.87)	0.39	1.27 (0.61-2.64)	0.52	1.19 (0.57-2.48)	0.65	
5-6 per week	6	2	1.06 (0.28-4.02)	0.93	1.10 (0.29-4.22)	0.89	1.29 (0.33-5.02)	0.71	
At least 1 per day	27	7	0.66 (0.31-1.41)	0.28	0.64 (0.30-1.37)	0.25	0.70 (0.32-1.50)	0.36	

Table 52 Hazard ratios (UD) and 05% confidence intervals (05% CL) for Coverence intervals hazard medals predicting a first resurrence of blodder sensor based on non-slopphile

Table S3. (continued)									
			Model 1*		Model 2**		Model 3***		
	n	events	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	p trend
Soup				•	• •				•
Never/less than 1 per month	219	70	ref		ref		ref		0.13
1-3 per month	167	66	1.27 (0.91-1.78)	0.16	1.27 (0.91-1.78)	0.16	1.27 (0.91-1.78)	0.17	
1 per week	141	47	1.07 (0.74-1.55)	0.70	1.02 (0.71-1.48)	0.91	1.02 (0.70-1.48)	0.91	
2-4 per week	148	47	1.07 (0.74-1.55)	0.71	1.03 (0.71-1.50)	0.88	1.03 (0.71-1.51)	0.86	
5-6 per week	18	3	0.49 (0.15-1.56)	0.23	0.46 (0.14-1.47)	0.19	0.44 (0.13-1.49)	0.19	
At least 1 per day	23	4	0.47 (0.17-1.32)	0.15	0.44 (0.16-1.22)	0.11	0.44 (0.17-1.15)	0.09	
Fizzy pop (e.g. lemonade, cola)									
Never/less than 1 per month	437	154	ref		ref		ref		0.49
1-3 per month	71	23	1.00 (0.64-1.57)	1.00	1.05 (0.67-1.65)	0.83	1.06 (0.67-1.67)	0.82	
1 per week	55	14	0.66 (0.39-1.13)	0.13	0.70 (0.41-1.20)	0.19	0.69 (0.41-1.17)	0.17	
2-4 per week	68	19	0.79 (0.49-1.28)	0.34	0.82 (0.51-1.33)	0.43	0.81 (0.50-1.31)	0.40	
5-6 per week	14	2	0.33 (0.08-1.35)	0.12	0.33 (0.08-1.32)	0.12	0.34 (0.08-1.47)	0.15	
At least 1 per day	71	25	1.03 (0.68-1.57)	0.88	1.05 (0.69-1.61)	0.81	1.08 (0.70-1.65)	0.73	
Pure fruit juice (e.g. orange, apple)									
Never/less than 1 per month	275	86	ref		ref		ref		0.38
1-3 per month	82	33	1.38 (0.94-2.03)	0.10	1.43 (0.97-2.11)	0.07	1.54 (1.05-2.26)	0.03	
1 per week	72	21	1.02 (0.62-1.66)	0.94	1.11 (0.67-1.81)	0.69	1.09 (0.67-1.78)	0.72	
2-4 per week	103	27	0.80 (0.52-1.24)	0.32	0.87 (0.56-1.35)	0.52	0.90 (0.57-1.40)	0.63	
5-6 per week	42	20	1.68 (1.01-2.80)	0.05	1.71 (1.03-2.84)	0.04	1.76 (1.04-2.98)	0.03	
At least 1 per day	142	50	1.14 (0.81-1.61)	0.45	1.15 (0.81-1.62)	0.43	1.18 (0.83-1.67)	0.35	
Fruit squash or cordial									
Never/less than 1 per month	390	129	ref		ref		ref		0.81
1-3 per month	60	19	0.92 (0.57-1.48)	0.72	0.91 (0.57-1.48)	0.71	1.04 (0.64-1.71)	0.87	
1 per week	64	17	0.80 (0.48-1.32)	0.39	0.82 (0.49-1.36)	0.43	0.83 (0.51-1.36)	0.46	
2-4 per week	72	25	1.04 (0.68-1.59)	0.86	1.06 (0.69-1.63)	0.78	1.03 (0.67-1.59)	0.90	
5-6 per week	29	10	1.01 (0.54-1.90)	0.97	1.03 (0.54-1.96)	0.93	1.10 (0.58-2.10)	0.77	
At least 1 per day	101	37	1.14 (0.79-1.64)	0.49	1.12 (0.77-1.61)	0.56	1.05 (0.73-1.51)	0.79	

Table S3. (continued)			Model 1*		Model 2**		Model 3***		
	n	events	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	p trend
Milk			, <i>,</i> ,	•	, <i>i</i>	•	· · · · · ·	•	
Never/less than 1 per month	432	148	ref		ref		ref		0.37
1-3 per month	51	16	0.79 (0.49-1.29)	0.35	0.82 (0.50-1.35)	0.44	0.77 (0.47-1.27)	0.31	
1 per week	31	11	1.03 (0.56-1.92)	0.92	1.05 (0.56-1.96)	0.88	0.97 (0.53-1.78)	0.92	
2-4 per week	50	19	1.09 (0.68-1.74)	0.73	1.18 (0.73-1.90)	0.50	1.29 (0.80-2.08)	0.29	
5-6 per week	27	7	0.64 (0.30-1.39)	0.26	0.68 (0.32-1.44)	0.31	0.68 (0.32-1.45)	0.31	
At least 1 per day	125	36	0.79 (0.55-1.14)	0.21	0.80 (0.56-1.16)	0.24	0.83 (0.57-1.20)	0.31	
Water (tap, filtered, or bottled)									
Never/less than 1 per month	86	35	ref		ref		ref		0.18
1-3 per month	25	8	0.83 (0.40-1.75)	0.63	0.86 (0.41-1.82)	0.69	0.83 (0.39-1.74)	0.62	
1 per week	33	11	0.80 (0.41-1.58)	0.53	0.82 (0.42-1.62)	0.56	0.77 (0.39-1.52)	0.45	
2-4 per week	47	17	0.92 (0.52-1.64)	0.78	0.97 (0.54-1.73)	0.91	0.83 (0.46-1.49)	0.53	
5-6 per week	51	14	0.73 (0.38-1.40)	0.34	0.79 (0.41-1.53)	0.49	0.80 (0.42-1.56)	0.52	
At least 1 per day	474	152	0.76 (0.53-1.09)	0.14	0.78 (0.54-1.14)	0.20	0.76 (0.52-1.10)	0.14	

			Model 1*		Model 2**		Model 3***		
	n	events	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	p trend
Coffee					· · · · ·	-		•	
Never/less than 1 per month	152	50	ref		ref		ref		0.52
1-3 per month	39	25	1.00 (0.83-1.21)	0.96	1.01 (0.84-1.21)	0.91	0.99 (0.83-1.19)	0.93	
1 per week	46	26	1.11 (0.81-1.52)	0.52	1.09 (0.79-1.50)	0.59	1.08 (0.78-1.50)	0.63	
2-4 per week	78	53	1.03 (0.87-1.23)	0.69	1.05 (0.88-1.25)	0.59	1.06 (0.88-1.26)	0.55	
5-6 per week	34	21	0.99 (0.74-1.31)	0.92	1.01 (0.76-1.34)	0.93	1.00 (0.76-1.33)	0.99	
At least 1 per day	367	209	0.99 (0.86-1.14)	0.89	0.99 (0.86-1.14)	0.93	0.98 (0.84-1.13)	0.73	
Теа			· · · · ·						
Never/less than 1 per month	73	34	ref		ref		ref		0.82
1-3 per month	11	7	1.65 (0.75-3.62)	0.21	1.73 (0.83-3.60)	0.14	1.61 (0.81-3.23)	0.18	
1 per week	1	0	-		-		-		
2-4 per week	13	15	1.14 (0.79-1.64)	0.50	1.16 (0.79-1.69)	0.44	1.11 (0.78-1.59)	0.56	
5-6 per week	24	17	1.05 (0.76-1.46)	0.76	1.08 (0.78-1.51)	0.63	1.02 (0.74-1.42)	0.89	
At least 1 per day	594	311	1.14 (0.90-1.45)	0.28	1.14 (0.90-1.45)	0.29	1.09 (0.86-1.38)	0.47	
Hot chocolate			· · ·						
Never/less than 1 per month	548	284	ref		ref		ref		0.74
1-3 per month	70	39	0.89 (0.77-1.04)	0.15	0.88 (0.75-1.03)	0.10	0.87 (0.74-1.02)	0.09	
1 per week	26	15	0.87 (0.70-1.07)	0.18	0.87 (0.70-1.08)	0.20	0.89 (0.73-1.10)	0.29	
2-4 per week	29	25	1.01 (0.80-1.29)	0.91	1.01 (0.78-1.29)	0.96	0.98 (0.76-1.27)	0.86	
5-6 per week	4	0	-		-		-		
At least 1 per day	39	21	1.07 (0.87-1.31)	0.52	1.06 (0.87-1.30)	0.58	1.01 (0.82-1.24)	0.94	
Ovaltine / horlicks									
Never/less than 1 per month	634	343	ref		ref		ref		0.25
1-3 per month	21	5	0.78 (0.66-0.92)	0.00	0.78 (0.67-0.91)	0.00	0.77 (0.67-0.89)	0.00	
1 per week	12	6	1.64 (0.82-3.25)	0.16	1.68 (0.83-3.38)	0.15	1.79 (0.87-3.67)	0.11	
2-4 per week	16	13	0.97 (0.78-1.22)	0.81	0.98 (0.78-1.24)	0.88	1.02 (0.82-1.26)	0.88	
5-6 per week	6	5	1.65 (1.32-2.06)	0.00	1.64 (1.32-2.03)	0.00	1.74 (1.41-2.15)	0.00	
At least 1 per day	27	12	1.10 (0.89-1.36)	0.39	1.03 (0.81-1.31)	0.80	0.98 (0.75-1.29)	0.89	

**T** 11 04 امام ما ما 

Table S4. (continued)									
			Model 1*		Model 2**		Model 3***		
	n	events	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	p trend
Soup									
Never/less than 1 per month	219	113	ref		ref		ref		0.37
1-3 per month	167	108	0.99 (0.86-1.15)	0.93	1.00 (0.86-1.16)	0.99	1.00 (0.86-1.16)	0.97	
1 per week	141	78	0.97 (0.85-1.12)	0.72	0.98 (0.85-1.14)	0.81	0.97 (0.84-1.12)	0.69	
2-4 per week	148	69	1.10 (0.93-1.29)	0.27	1.09 (0.92-1.29)	0.30	1.08 (0.92-1.27)	0.34	
5-6 per week	18	10	0.79 (0.64-0.97)	0.03	0.79 (0.64-0.99)	0.04	0.85 (0.67-1.07)	0.16	
At least 1 per day	23	6	1.70 (0.94-3.09)	0.08	1.68 (0.94-3.00)	0.08	1.63 (0.97-2.74)	0.07	
Fizzy pop (e.g. lemonade, cola)									
Never/less than 1 per month	437	246	ref		ref		ref		0.33
1-3 per month	71	38	0.94 (0.78-1.15)	0.57	0.96 (0.79-1.17)	0.68	0.96 (0.80-1.16)	0.68	
1 per week	55	24	1.03 (0.86-1.22)	0.76	1.04 (0.87-1.24)	0.70	1.02 (0.85-1.22)	0.83	
2-4 per week	68	34	1.01 (0.85-1.19)	0.93	1.03 (0.87-1.22)	0.73	1.05 (0.88-1.26)	0.58	
5-6 per week	14	2	0.78 (0.68-0.90)	0.00	0.84 (0.71-0.99)	0.04	0.79 (0.64-0.98)	0.03	
At least 1 per day	71	40	1.11 (0.92-1.33)	0.29	1.11 (0.93-1.33)	0.25	1.09 (0.91-1.31)	0.33	
Pure fruit juice (e.g. orange, apple)									
Never/less than 1 per month	275	142	ref		ref		ref		0.43
1-3 per month	82	53	0.93 (0.79-1.09)	0.39	0.92 (0.78-1.08)	0.32	0.95 (0.81-1.11)	0.51	
1 per week	72	36	1.02 (0.83-1.24)	0.88	1.01 (0.83-1.24)	0.89	1.00 (0.82-1.22)	0.98	
2-4 per week	103	35	1.09 (0.90-1.33)	0.37	1.12 (0.92-1.36)	0.27	1.12 (0.91-1.37)	0.29	
5-6 per week	42	39	0.91 (0.75-1.11)	0.36	0.90 (0.73-1.11)	0.32	0.94 (0.76-1.15)	0.55	
At least 1 per day	142	79	0.91 (0.78-1.06)	0.21	0.90 (0.78-1.05)	0.18	0.92 (0.80-1.06)	0.27	
Fruit squash or cordial									
Never/less than 1 per month	390	213	ref		ref		ref		0.39
1-3 per month	60	29	0.93 (0.76-1.14)	0.49	0.91 (0.75-1.11)	0.35	0.92 (0.77-1.11)	0.40	
1 per week	64	18	1.19 (0.92-1.52)	0.18	1.16 (0.90-1.50)	0.24	1.13 (0.87-1.47)	0.36	
2-4 per week	72	40	1.01 (0.86-1.19)	0.87	1.00 (0.85-1.19)	0.97	0.97 (0.82-1.16)	0.75	
5-6 per week	29	21	1.02 (0.78-1.33)	0.90	1.04 (0.78-1.38)	0.79	1.04 (0.79-1.37)	0.79	
At least 1 per day	101	63	1.10 (0.93-1.29)	0.27	1.08 (0.92-1.27)	0.34	1.08 (0.92-1.26)	0.35	

Table S4. (continued)									
			Model 1*		Model 2**		Model 3***		
	n	events	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	p trend
Milk									
Never/less than 1 per month	432	241	ref		ref		ref		0.25
1-3 per month	51	20	0.92 (0.79-1.07)	0.30	0.94 (0.81-1.09)	0.42	0.97 (0.83-1.12)	0.66	
1 per week	31	21	1.13 (0.88-1.45)	0.33	1.13 (0.87-1.47)	0.37	1.14 (0.86-1.50)	0.36	
2-4 per week	50	36	0.80 (0.71-0.91)	0.00	0.80 (0.70-0.92)	0.00	0.79 (0.68-0.92)	0.00	
5-6 per week	27	20	0.87 (0.66-1.14)	0.30	0.89 (0.66-1.19)	0.43	0.92 (0.68-1.24)	0.58	
At least 1 per day	125	46	1.01 (0.87-1.17)	0.90	1.00 (0.86-1.16)	1.00	0.98 (0.85-1.14)	0.83	
Water (tap, filtered, or bottled)									
Never/less than 1 per month	86	49	ref		ref		ref		0.33
1-3 per month	25	14	0.80 (0.67-0.96)	0.02	0.83 (0.68-1.00)	0.05	0.86 (0.71-1.03)	0.10	
1 per week	33	21	0.69 (0.53-0.89)	0.00	0.68 (0.52-0.89)	0.01	0.71 (0.55-0.91)	0.01	
2-4 per week	47	35	0.97 (0.79-1.19)	0.75	0.97 (0.79-1.20)	0.81	0.98 (0.79-1.22)	0.89	
5-6 per week	51	35	0.91 (0.72-1.14)	0.40	0.93 (0.73-1.17)	0.54	0.94 (0.74-1.19)	0.61	
At least 1 per day	474	230	0.99 (0.83-1.17)	0.89	1.00 (0.84-1.18)	0.96	1.01 (0.85-1.20)	0.91	

#### Post-diagnosis analysis

			Model 1*		Model 2**		Model 3***		
	n	Events	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p- value	p trend
Total alcohol*									
T1 (0 mL/day)	87	32	ref		ref		ref		0.94
T2 (25 mL-125 mL/day)	130	49	0.96 (0.62-1.50)	0.85	0.97 (0.62-1.51)	0.88	0.97 (0.62-1.51)	0.89	
T3 (>125 mL/day)	162	58	0.93 (0.61-1.44)	0.76	0.94 (0.60-1.47)	0.79	1.01 (0.65-1.58)	0.96	
Beer (e.g. beer, lager, stout)									
Never/less than 1 per month	169	65	ref		ref		ref		0.93
1-3 per month	39	14	0.86 (0.49-1.50)	0.58	0.82 (0.46-1.45)	0.49	0.94 (0.53-1.65)	0.82	
1 per week	43	15	0.86 (0.49-1.52)	0.60	0.90 (0.50-1.60)	0.71	1.00 (0.55-1.81)	0.99	
2-4 per week	60	21	0.87 (0.53-1.41)	0.57	0.84 (0.51-1.38)	0.48	1.00 (0.60-1.69)	0.99	
5-6 per week	24	6	0.58 (0.25-1.33)	0.20	0.56 (0.24-1.35)	0.20	0.65 (0.26-1.65)	0.37	
At least 1 per day	44	18	1.08 (0.64-1.82)	0.78	1.03 (0.59-1.79)	0.92	1.05 (0.60-1.84)	0.86	
Cider									
Never/less than 1 per month	356	129	ref		ref		ref		0.21
1-3 per month	15	7	1.45 (0.66-3.19)	0.35	1.60 (0.75-3.40)	0.23	1.43 (0.68-3.04)	0.35	
1 per week	3	0	-		-		-		
2-4 per week	3	2	2.54 (0.55-11.79)	0.23	2.86 (0.68-11.99)	0.15	4.57 (2.11-9.87)	0.00	
5-6 per week	1	1	4.28 (3.41-5.37)	0.00	3.91 (2.99-5.10)	0.00	5.70 (2.71-12.00)	0.00	
At least 1 per day	1	0	-		-		-		
Wine or champagne									
Never/less than 1 per month	202	75	ref		ref		ref		0.36
1-3 per month	27	8	0.78 (0.38-1.63)	0.51	0.87 (0.41-1.84)	0.72	0.80 (0.38-1.65)	0.54	
1 per week	37	15	1.14 (0.65-2.00)	0.66	1.19 (0.68-2.11)	0.54	1.11 (0.63-1.93)	0.72	
2-4 per week	61	18	0.76 (0.45-1.28)	0.30	0.81 (0.47-1.39)	0.45	0.89 (0.52-1.55)	0.69	
5-6 per week	12	6	1.38 (0.61-3.09)	0.44	1.46 (0.68-3.15)	0.33	1.89 (0.83-4.30)	0.13	
At least 1 per day	40	17	1.21 (0.71-2.07)	0.48	1.26 (0.74-2.13)	0.40	1.29 (0.74-2.24)	0.37	

\*Q1 includes non-drinkers only, Q2 includes drinkers whose consumption corresponds with up to 1 large glass of wine or half a pint of beer/lager per day, Q3 includes drinkers whose consumption corresponds with more than 1 large glass of wine or half a pint of beer/cider per day. \*Model 1 was unadjusted, \*\*Model 2 was adjusted for age, sex, and smoking status, \*\*\*Model 3 was adjusted for age, sex, smoking status, and tumour stage, grade, size and multiplicity.

Table S5. (continued)									
· · · · · ·			Model 1*		Model 2**		Model 3***		
	n	events	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p- value	p trend
Fortified wine (e.g. port, sherry, cinzano)									
Never/less than 1 per month	339	124	ref		ref		ref		0.55
1-3 per month	23	11	1.38 (0.73-2.60)	0.33	1.42 (0.76-2.68)	0.28	1.53 (0.84-2.80)	0.16	
1 per week	10	2	0.49 (0.13-1.87)	0.30	0.53 (0.14-1.98)	0.35	0.52 (0.15-1.79)	0.30	
2-4 per week	5	2	0.86 (0.27-2.75)	0.80	0.91 (0.33-2.50)	0.85	0.83 (0.29-2.34)	0.72	
5-6 per week	1	0	-		-		-		
At least 1 per day	1	0	-		-		-		
Spirits (e.g. gin, brandy, rum, vodka, whiskey)									
Never/less than 1 per month	243	90	ref		ref		ref		0.39
1-3 per month	45	16	0.96 (0.55-1.68)	0.88	0.94 (0.54-1.64)	0.84	1.01 (0.58-1.76)	0.98	
1 per week	19	10	1.46 (0.78-2.71)	0.23	1.44 (0.77-2.72)	0.25	1.39 (0.75-2.58)	0.30	
2-4 per week	42	14	0.88 (0.50-1.53)	0.64	0.86 (0.49-1.49)	0.59	0.81 (0.46-1.44)	0.48	
5-6 per week	9	4	1.12 (0.47-2.66)	0.80	1.07 (0.43-2.67)	0.89	1.30 (0.49-3.41)	0.60	
At least 1 per day	21	5	0.59 (0.25-1.41)	0.24	0.56 (0.24-1.33)	0.19	0.59 (0.26-1.35)	0.21	
Liqueurs (e.g. tia maria, baileys, cointreau)									
Never/less than 1 per month	359	130	ref		ref		ref		0.82
1-3 per month	12	5	1.07 (0.48-2.39)	0.88	0.98 (0.45-2.17)	0.97	0.92 (0.40-2.14)	0.85	
1 per week	2	2	15.71 (5.23-47.15)	0.00	18.43 (5.62-60.43)	0.00	15.62 (4.21-58.01)	0.00	
2-4 per week	4	1	0.69 (0.09-5.36)	0.73	0.70 (0.09-5.24)	0.73	0.70 (0.12-4.18)	0.69	
5-6 per week	0	0	-		-		-		
At least 1 per day	2	1	1.42 (0.20-10.29)	0.73	1.21 (0.16-8.86)	0.85	0.94 (0.08-11.14)	0.96	

Table S6. Hazard ratios (HR) and 95% cor and beverage-specific alcohol intake 1 ye			) for Cox proportional	hazard models	s predicting multiple re	currences of	bladder cancer, bas	sed on tot	al alcohol
		313 (II-077)	Model 1*		Model 2**		Model 3***		
	n	events	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p- value	p trend
Total alcohol*									
T1 (0 mL/day)	87	79	ref		ref		ref		0.42
T2 (25 mL-125 mL/day)	130	124	0.91 (0.77-1.09)	0.31	0.90 (0.76-1.08)	0.26	0.93 (0.78-1.10)	0.38	
T3 (>125 mL/day)	162	142	1.06 (0.89-1.27)	0.50	1.03 (0.86-1.23)	0.75	1.05 (0.88-1.25)	0.60	
Beer (e.g. beer, lager, stout)									
Never/less than 1 per month	169	97	ref		ref		ref		0.09
1-3 per month	39	15	0.93 (0.79-1.10)	0.39	0.92 (0.75-1.13)	0.44	0.92 (0.74-1.15)	0.46	
1 per week	43	29	1.23 (0.97-1.56)	0.08	1.27 (0.99-1.64)	0.06	1.31 (1.03-1.65)	0.03	
2-4 per week	60	30	1.11 (0.92-1.34)	0.29	1.10 (0.89-1.36)	0.39	1.06 (0.88-1.29)	0.54	
5-6 per week	24	6	1.17 (0.79-1.73)	0.45	1.16 (0.77-1.74)	0.48	1.16 (0.74-1.82)	0.52	
At least 1 per day	44	36	1.18 (0.99-1.41)	0.07	1.16 (0.96-1.40)	0.13	1.16 (0.95-1.41)	0.16	
Cider			X /						
Never/less than 1 per month	356	197	ref		ref		ref		0.94
1-3 per month	15	11	1.13 (0.88-1.44)	0.34	1.06 (0.80-1.40)	0.68	1.00 (0.75-1.33)	0.99	
1 per week	3	0	-		-		-		
2-4 per week	3	4	0.75 (0.51-1.09)	0.13	0.74 (0.50-1.08)	0.11	0.83 (0.56-1.23)	0.36	
5-6 per week	1	1	2.45 (1.93-3.10)	0.00	2.36 (1.85-3.01)	0.00	2.47 (1.53-3.96)	0.00	
At least 1 per day	1	0	-		-		-		
Wine or champagne									
Never/less than 1 per month	202	113	ref		ref		ref		0.35
1-3 per month	27	21	0.87 (0.69-1.10)	0.24	0.86 (0.69-1.08)	0.19	0.88 (0.71-1.09)	0.24	
1 per week	37	22	1.07 (0.91-1.27)	0.39	1.06 (0.90-1.25)	0.51	1.09 (0.90-1.31)	0.38	
2-4 per week	61	25	1.02 (0.82-1.28)	0.84	1.03 (0.82-1.29)	0.79	1.11 (0.89-1.39)	0.35	
5-6 per week	12	9	0.80 (0.54-1.18)	0.26	0.77 (0.53-1.12)	0.17	0.80 (0.55-1.18)	0.26	
At least 1 per day	40	23	1.16 (0.90-1.49)	0.25	1.17 (0.91-1.51)	0.22	1.16 (0.90-1.50)	0.26	

\*Q1 includes non-drinkers only, Q2 includes drinkers whose consumption corresponds with up to 1 large glass of wine or half a pint of beer/lager per day, Q3 includes drinkers whose consumption corresponds with more than 1 large glass of wine or half a pint of beer/cider per day. \*Model 1 was unadjusted, \*\*Model 2 was adjusted for age, sex, and smoking status, \*\*\*Model 3 was adjusted for age, sex, smoking status, and tumour stage, grade, size and multiplicity, and

re-resection of a bladder tumour (second transurethral resection).

Table S6. (continued)									
			Model 1*		Model 2**		Model 3***		
	n	events	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p- value	p trend
Fortified wine (e.g. port, sherry, cinzano)									
Never/less than 1 per month	339	194	ref		ref		ref		0.35
1-3 per month	23	13	1.04 (0.80-1.35)	0.76	1.07 (0.83-1.39)	0.60	1.08 (0.84-1.38)	0.55	
1 per week	10	4	0.60 (0.36-1.01)	0.05	0.60 (0.36-1.03)	0.06	0.62 (0.36-1.07)	0.09	
2-4 per week	5	2	0.86 (0.64-1.14)	0.30	0.92 (0.63-1.35)	0.68	0.90 (0.63-1.30)	0.58	
5-6 per week	1	0	-		-		-		
At least 1 per day	1	0	-		-		-		
Spirits (e.g. gin, brandy, rum, vodka, whiskey)									
Never/less than 1 per month	243	142	ref		ref		ref		0.55
1-3 per month	45	34	0.94 (0.77-1.15)	0.54	0.93 (0.77-1.13)	0.49	0.92 (0.77-1.11)	0.41	
1 per week	19	11	0.99 (0.84-1.16)	0.87	1.02 (0.87-1.20)	0.82	0.95 (0.75-1.20)	0.66	
2-4 per week	42	15	1.07 (0.87-1.31)	0.53	1.10 (0.89-1.36)	0.39	1.08 (0.86-1.35)	0.52	
5-6 per week	9	6	1.14 (0.82-1.61)	0.43	1.10 (0.79-1.54)	0.57	1.13 (0.81-1.59)	0.48	
At least 1 per day	21	5	0.99 (0.67-1.46)	0.95	1.01 (0.67-1.53)	0.96	1.08 (0.70-1.68)	0.73	
Liqueurs (e.g. tia maria, baileys, cointreau)			, <i>i</i>						
Never/less than 1 per month	359	202	ref		ref		ref		0.85
1-3 per month	12	5	0.88 (0.64-1.21)	0.44	0.92 (0.66-1.29)	0.64	0.90 (0.65-1.24)	0.52	
1 per week	2	3	1.06 (0.58-1.94)	0.84	1.11 (0.62-1.97)	0.73	0.93 (0.51-1.71)	0.82	
2-4 per week	4	2	1.03 (0.77-1.37)	0.84	1.06 (0.79-1.43)	0.70	1.10 (0.79-1.52)	0.57	
5-6 per week	0	0	-		-		-		
At least 1 per day	2	1	0.83 (0.75-0.92)	0.00	0.91 (0.76-1.08)	0.27	0.97 (0.79-1.17)	0.73	

			Model 1*		Model 2**		Model 3***		
	n	events	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p- value	p trend
Coffee									
Never/less than 1 per month	80	23	ref		ref		ref		0.13
1-3 per month	20	7	1.30 (0.54-3.13)	0.55	1.33 (0.56-3.19)	0.52	1.02 (0.41-2.51)	0.97	
1 per week	24	9	1.40 (0.65-3.02)	0.39	1.51 (0.70-3.29)	0.29	1.39 (0.62-3.16)	0.43	
2-4 per week	31	13	1.57 (0.78-3.16)	0.21	1.59 (0.79-3.20)	0.19	1.55 (0.75-3.20)	0.24	
5-6 per week	6	2	1.21 (0.30-4.81)	0.79	1.29 (0.35-4.74)	0.71	0.87 (0.26-2.95)	0.83	
At least 1 per day	218	85	1.37 (0.86-2.19)	0.18	1.42 (0.89-2.27)	0.14	1.44 (0.89-2.31)	0.14	
Теа			, ,		. ,				
Never/less than 1 per month	37	15	ref		ref		ref		0.74
1-3 per month	1	0	-		-		-		
1 per week	7	3	1.29 (0.35-4.81)	0.70	1.43 (0.40-5.10)	0.58	1.87 (0.60-5.89)	0.28	
2-4 per week	13	7	1.42 (0.64-3.13)	0.39	1.74 (0.80-3.80)	0.16	2.03 (0.91-4.53)	0.08	
5-6 per week	8	3	1.01 (0.35-2.90)	0.99	1.10 (0.41-2.96)	0.85	1.11 (0.41-3.03)	0.84	
At least 1 per day	313	111	1.00 (0.61-1.64)	0.99	1.03 (0.63-1.69)	0.89	1.18 (0.71-1.97)	0.53	
Hot chocolate									
Never/less than 1 per month	311	115	ref		ref		ref		0.15
1-3 per month	22	10	1.32 (0.70-2.49)	0.40	1.36 (0.74-2.50)	0.32	1.11 (0.63-1.95)	0.72	
1 per week	17	5	0.74 (0.31-1.74)	0.49	0.76 (0.33-1.75)	0.51	0.55 (0.24-1.26)	0.16	
2-4 per week	15	6	1.07 (0.49-2.36)	0.86	1.06 (0.48-2.36)	0.88	0.86 (0.37-2.01)	0.73	
5-6 per week	0	0	-		-		-		
At least 1 per day	14	3	0.53 (0.17-1.63)	0.27	0.50 (0.16-1.59)	0.24	0.50 (0.15-1.62)	0.24	
Ovaltine / Horlicks									
Never/less than 1 per month	332	119	ref		ref		ref		0.67
1-3 per month	11	6	1.82 (0.80-4.15)	0.16	1.89 (0.84-4.22)	0.12	1.71 (0.78-3.76)	0.18	
1 per week	3	0	-		-		-		
2-4 per week	12	6	1.68 (0.75-3.75)	0.21	1.55 (0.69-3.46)	0.29	1.09 (0.48-2.51)	0.83	
5-6 per week	2	1	1.99 (0.20-20.10)	0.56	1.78 (0.18-18.07)	0.62	1.57 (0.15-16.70)	0.71	
At least 1 per day	19	7	1.05 (0.49-2.25)	0.89	1.11 (0.51-2.39)	0.80	1.13 (0.52-2.45)	0.76	

Table S7. Hazard ratios (HD) and 05% confidence intervals (05% C1) for Cox proportional bazard models predicting a first recurrence of bladder cancer, based on pop alcoholic

Table S7. (continued)									
			Model 1*		Model 2**		Model 3***		
	n	events	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p- value	p trend
Soup									
Never/less than 1 per month	103	33	ref		ref		ref		0.59
1-3 per month	101	44	1.50 (0.96-2.34)	0.08	1.54 (0.98-2.42)	0.06	1.53 (0.97-2.39)	0.07	
1 per week	80	30	1.27 (0.77-2.09)	0.35	1.29 (0.78-2.12)	0.32	1.36 (0.81-2.27)	0.24	
2-4 per week	77	26	1.17 (0.69-1.97)	0.57	1.17 (0.68-1.99)	0.57	1.20 (0.70-2.08)	0.51	
5-6 per week	9	3	1.24 (0.35-4.44)	0.74	1.31 (0.38-4.52)	0.67	1.72 (0.53-5.60)	0.37	
At least 1 per day	9	3	1.05 (0.34-3.26)	0.94	1.11 (0.38-3.21)	0.85	1.01 (0.38-2.66)	0.98	
Fizzy pop (e.g. lemonade, cola)									
Never/less than 1 per month	251	95	ref		ref		ref		0.49
1-3 per month	23	6	0.62 (0.28-1.37)	0.24	0.62 (0.27-1.39)	0.25	0.53 (0.21-1.30)	0.17	
1 per week	23	9	1.05 (0.53-2.10)	0.88	1.02 (0.51-2.05)	0.96	0.80 (0.41-1.53)	0.50	
2-4 per week	38	14	0.97 (0.54-1.75)	0.92	0.97 (0.54-1.73)	0.92	0.96 (0.53-1.75)	0.90	
5-6 per week	10	3	0.77 (0.27-2.21)	0.62	0.73 (0.26-2.09)	0.56	0.82 (0.26-2.53)	0.72	
At least 1 per day	34	12	0.88 (0.50-1.54)	0.65	0.84 (0.48-1.50)	0.56	0.81 (0.45-1.47)	0.50	
Pure fruit juice (e.g. orange, apple)									
Never/less than 1 per month	144	44	ref		ref		ref		0.92
1-3 per month	33	21	2.28 (1.41-3.70)	0.00	2.25 (1.39-3.66)	0.00	2.21 (1.39-3.53)	0.00	
1 per week	38	18	1.73 (0.98-3.07)	0.06	1.76 (0.98-3.16)	0.06	1.88 (1.06-3.35)	0.03	
2-4 per week	55	19	1.09 (0.64-1.84)	0.76	1.07 (0.64-1.80)	0.78	1.10 (0.65-1.86)	0.71	
5-6 per week	3	1	1.02 (0.13-8.29)	0.98	1.13 (0.15-8.47)	0.91	0.91 (0.18-4.48)	0.91	
At least 1 per day	106	36	1.07 (0.69-1.68)	0.76	1.07 (0.68-1.68)	0.77	1.17 (0.73-1.86)	0.51	
Fruit squash or cordial									
Never/less than 1 per month	202	73	ref		ref		ref		0.35
1-3 per month	20	4	0.49 (0.18-1.33)	0.16	0.47 (0.17-1.30)	0.15	0.52 (0.20-1.36)	0.18	
1 per week	32	12	1.05 (0.56-1.97)	0.88	1.07 (0.58-2.00)	0.82	0.99 (0.55-1.81)	0.99	
2-4 per week	37	12	0.83 (0.45-1.51)	0.54	0.78 (0.43-1.43)	0.43	0.79 (0.44-1.43)	0.43	
5-6 per week	6	2	0.96 (0.23-4.04)	0.95	0.87 (0.20-3.73)	0.85	0.93 (0.21-4.21)	0.93	
At least 1 per day	82	36	1.19 (0.81-1.76)	0.38	1.21 (0.81-1.80)	0.36	1.26 (0.85-1.88)	0.25	

Table S7. (continued)			-	-	-				-
			Model 1*		Model 2**		Model 3***		
	n	events	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p- value	p trend
Milk									
Never/less than 1 per month	273	107	ref		ref		ref		0.39
1-3 per month	12	3	0.58 (0.20-1.72)	0.33	0.57 (0.19-1.71)	0.32	0.47 (0.17-1.31)	0.15	
1 per week	8	2	0.67 (0.15-3.01)	0.60	0.80 (0.17-3.72)	0.78	0.84 (0.17-4.21)	0.83	
2-4 per week	28	7	0.58 (0.27-1.22)	0.15	0.58 (0.28-1.22)	0.15	0.65 (0.31-1.38)	0.26	
5-6 per week	5	3	1.63 (0.70-3.80)	0.26	1.64 (0.73-3.68)	0.23	1.41 (0.56-3.57)	0.47	
At least 1 per day	53	17	0.80 (0.47-1.35)	0.40	0.81 (0.47-1.39)	0.44	0.81 (0.46-1.42)	0.45	
Water (tap, filtered, or bottled)									
Never/less than 1 per month	50	22	ref		ref		ref		0.27
1-3 per month	5	2	0.74 (0.18-3.06)	0.68	0.72 (0.16-3.23)	0.66	0.84 (0.21-3.34)	0.81	
1 per week	9	4	1.14 (0.36-3.62)	0.82	1.16 (0.36-3.72)	0.80	1.19 (0.47-3.06)	0.71	
2-4 per week	25	10	0.76 (0.37-1.58)	0.47	0.79 (0.38-1.65)	0.53	1.00 (0.47-2.14)	1.00	
5-6 per week	11	4	0.68 (0.26-1.78)	0.43	0.69 (0.27-1.77)	0.44	0.63 (0.26-1.48)	0.29	
At least 1 per day	279	97	0.70 (0.45-1.11)	0.13	0.75 (0.47-1.22)	0.25	0.79 (0.49-1.28)	0.34	

Table S8. Hazard ratios (HR) and 95% c alcoholic beverage intake 1 year after d			I.) for Cox proportional	nazard models	s predicting multiple red	currences of a	bladder cancer, base	ed on nor	1-
<u> </u>			Model 1*		Model 2**		Model 3***		
	n	events	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p- value	p trend
Coffee									
Never/less than 1 per month	80	33	ref		ref		ref		0.97
1-3 per month	20	14	0.96 (0.77-1.20)	0.72	0.94 (0.76-1.17)	0.57	0.96 (0.79-1.17)	0.70	
1 per week	24	13	1.15 (0.80-1.64)	0.44	1.10 (0.75-1.61)	0.64	1.02 (0.69-1.51)	0.92	
2-4 per week	31	23	0.98 (0.77-1.25)	0.87	0.99 (0.78-1.26)	0.95	1.03 (0.81-1.31)	0.83	
5-6 per week	6	4	0.88 (0.53-1.47)	0.63	0.92 (0.56-1.53)	0.75	0.79 (0.45-1.37)	0.40	
At least 1 per day	218	126	1.00 (0.85-1.19)	0.98	1.00 (0.85-1.18)	0.98	0.99 (0.83-1.17)	0.90	
Tea									
Never/less than 1 per month	37	22	ref		ref		ref		0.92
1-3 per month	1	0	-		-		-		
1 per week	7	7	1.47 (0.81-2.67)	0.20	1.47 (0.78-2.75)	0.23	1.31 (0.65-2.65)	0.45	
2-4 per week	13	8	1.28 (0.88-1.85)	0.20	1.24 (0.85-1.80)	0.26	1.11 (0.79-1.56)	0.55	
5-6 per week	8	7	0.86 (0.55-1.32)	0.49	0.89 (0.59-1.35)	0.59	0.81 (0.52-1.25)	0.34	
At least 1 per day	313	169	1.18 (0.89-1.56)	0.25	1.17 (0.88-1.56)	0.29	1.06 (0.80-1.42)	0.68	
Hot chocolate									
Never/less than 1 per month	311	170	ref		ref		ref		0.20
1-3 per month	22	20	0.92 (0.71-1.19)	0.53	0.93 (0.72-1.18)	0.53	0.86 (0.65-1.13)	0.27	
1 per week	17	10	0.79 (0.63-1.00)	0.05	0.83 (0.66-1.04)	0.10	0.79 (0.62-1.02)	0.07	
2-4 per week	15	9	0.96 (0.72-1.28)	0.78	0.97 (0.73-1.29)	0.83	0.95 (0.73-1.25)	0.73	
5-6 per week	0	0	-		-		-		
At least 1 per day	14	4	0.94 (0.70-1.26)	0.68	1.00 (0.73-1.35)	0.98	0.88 (0.59-1.31)	0.53	
Ovaltine / Horlicks									
Never/less than 1 per month	332	177	ref		ref		ref		0.20
1-3 per month	11	7	1.28 (0.87-1.88)	0.21	1.28 (0.84-1.95)	0.25	1.23 (0.82-1.86)	0.32	
1 per week	3	0	-		-		-		
2-4 per week	12	16	1.04 (0.75-1.45)	0.79	1.11 (0.79-1.55)	0.55	1.09 (0.78-1.53)	0.60	
5-6 per week	2	2	1.09 (0.93-1.28)	0.27	1.12 (0.95-1.32)	0.17	0.92 (0.74-1.15)	0.47	
At least 1 per day	19	11	1.17 (0.85-1.61)	0.33	1.23 (0.89-1.72)	0.21	1.23 (0.89-1.69)	0.21	

**T T T** ( ) ) ) ) )

Table S8. (continued)									
			Model 1*		Model 2**		Model 3***		
	n	events	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p- value	p trend
Soup									
Never/less than 1 per month	103	49	ref		ref		ref		0.28
1-3 per month	101	63	0.91 (0.77-1.06)	0.23	0.91 (0.78-1.07)	0.27	0.87 (0.74-1.02)	0.09	
1 per week	80	37	0.95 (0.79-1.13)	0.56	0.98 (0.82-1.16)	0.78	0.94 (0.79-1.13)	0.50	
2-4 per week	77	57	1.02 (0.81-1.29)	0.85	1.08 (0.86-1.35)	0.51	1.07 (0.88-1.31)	0.49	
5-6 per week	9	4	0.97 (0.72-1.31)	0.84	1.06 (0.75-1.50)	0.72	1.09 (0.76-1.58)	0.64	
At least 1 per day	9	3	1.03 (0.74-1.43)	0.87	1.18 (0.84-1.66)	0.35	1.01 (0.69-1.48)	0.96	
Fizzy pop (e.g. lemonade, cola)									
Never/less than 1 per month	251	146	ref		ref		ref		0.06
1-3 per month	23	11	1.16 (0.80-1.67)	0.44	1.15 (0.82-1.61)	0.42	1.09 (0.77-1.55)	0.63	
1 per week	23	13	1.04 (0.81-1.33)	0.77	1.00 (0.77-1.29)	0.99	0.99 (0.76-1.29)	0.95	
2-4 per week	38	23	0.94 (0.78-1.12)	0.47	0.88 (0.73-1.06)	0.19	0.89 (0.75-1.07)	0.23	
5-6 per week	10	3	0.99 (0.72-1.36)	0.96	0.98 (0.75-1.28)	0.89	0.98 (0.77-1.26)	0.90	
At least 1 per day	34	17	0.83 (0.69-0.99)	0.04	0.84 (0.70-1.01)	0.06	0.84 (0.70-1.01)	0.07	
Pure fruit juice (e.g. orange, apple)									
Never/less than 1 per month	144	69	ref		ref		ref		0.62
1-3 per month	33	34	0.97 (0.81-1.16)	0.76	0.98 (0.83-1.17)	0.86	0.99 (0.83-1.19)	0.95	
1 per week	38	25	1.20 (1.00-1.44)	0.05	1.19 (0.98-1.44)	0.08	1.17 (0.97-1.42)	0.10	
2-4 per week	55	31	0.94 (0.78-1.13)	0.50	0.95 (0.80-1.14)	0.61	1.01 (0.83-1.23)	0.92	
5-6 per week	3	1	1.52 (1.25-1.85)	0.00	1.56 (1.27-1.92)	0.00	1.59 (1.14-2.22)	0.01	
At least 1 per day	106	53	1.01 (0.84-1.22)	0.90	1.01 (0.84-1.22)	0.92	1.05 (0.86-1.27)	0.65	
Fruit squash or cordial									
Never/less than 1 per month	202	114	ref		ref		ref		1.00
1-3 per month	20	6	1.18 (0.79-1.75)	0.42	1.18 (0.79-1.76)	0.42	1.14 (0.79-1.64)	0.48	 
1 per week	32	25	1.19 (0.95-1.49)	0.13	1.18 (0.94-1.46)	0.15	1.15 (0.93-1.43)	0.21	 
2-4 per week	37	17	0.96 (0.75-1.23)	0.75	0.96 (0.74-1.24)	0.74	0.90 (0.69-1.18)	0.46	 
5-6 per week	6	3	0.72 (0.57-0.91)	0.01	0.76 (0.59-0.99)	0.04	0.77 (0.62-0.95)	0.02	 
At least 1 per day	82	48	1.01 (0.85-1.20)	0.90	1.02 (0.85-1.21)	0.85	1.03 (0.87-1.23)	0.72	 I

Table S8. (continued)									
			Model 1*		Model 2**		Model 3***		
	n	events	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p- value	p trend
Milk									
Never/less than 1 per month	273	160	ref		ref		ref		0.35
1-3 per month	12	4	1.10 (0.79-1.53)	0.57	1.05 (0.73-1.50)	0.80	1.09 (0.85-1.41)	0.50	
1 per week	8	2	2.08 (1.39-3.12)	0.00	2.01 (1.37-2.96)	0.00	1.92 (1.39-2.65)	0.00	
2-4 per week	28	10	0.95 (0.72-1.26)	0.74	0.94 (0.72-1.24)	0.66	0.89 (0.66-1.20)	0.46	
5-6 per week	5	4	0.74 (0.60-0.92)	0.01	0.76 (0.63-0.92)	0.00	0.76 (0.57-1.02)	0.06	
At least 1 per day	53	33	1.15 (0.94-1.42)	0.18	1.16 (0.95-1.42)	0.14	1.19 (0.96-1.46)	0.11	
Water (tap, filtered, or bottled)									
Never/less than 1 per month	50	32	ref		ref		ref		0.57
1-3 per month	5	2	0.79 (0.64-0.98)	0.03	0.74 (0.54-1.00)	0.05	0.90 (0.68-1.19)	0.47	
1 per week	9	10	0.98 (0.71-1.36)	0.91	0.94 (0.67-1.31)	0.70	1.01 (0.69-1.47)	0.96	
2-4 per week	25	12	0.89 (0.68-1.16)	0.38	0.89 (0.68-1.17)	0.41	0.90 (0.68-1.19)	0.48	
5-6 per week	11	6	0.80 (0.60-1.08)	0.15	0.80 (0.59-1.08)	0.14	0.72 (0.51-1.02)	0.07	
At least 1 per day	279	151	0.99 (0.83-1.18)	0.87	0.97 (0.81-1.16)	0.76	1.04 (0.86-1.26)	0.66	