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Fluid intake, genetic variants of UDP-glucuronosyltransferases, and bladder cancer risk

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Background: Results of studies of fluid consumption and its association with bladder cancer have been inconsistent. Few studies have considered modification effects from genetic variants that may interact with the type of consumed fluids. UDP-glucuronosyltransferases (UGTs), which are membrane-bound conjugating enzymes, catalyse the transformation of hydrophobic substrates to more water-soluble glucuronides to facilitate renal or biliary excretion. Whether genetic variants in UGTs could modulate the association between fluid intake and bladder cancer has not been studied.

Methods: We conducted a case–control study with 1007 patients with histopathologically confirmed bladder cancer and 1299 healthy matched controls. Fluid intake and epidemiologic data were collected via in-person interview. Multivariate unconditional logistic regression was used to estimate odds ratios (ORs) and the 95% confidence intervals (95% CI).

Results: After adjustment for potential confounders, high quantity of total fluid intake ($\geqslant$2789 *vs* $<$1696 ml per day) conferred a 41% increased risk of bladder cancer (OR = 1.41; 95% CI = 1.10–1.81). Specific fluids such as regular soft drinks and decaffeinated coffee were also associated with increased risks, whereas tea, wine, and liquor were associated with decreased risks. Among 83 single-nucleotide polymorphisms in the UGT gene family, 18 were significantly associated with bladder cancer risk. The most significant one was rs7571337, with the variant genotype conferring a 29% reduction in risk (OR = 0.71; 95% CI = 0.56–0.90).

Conclusions: Total and specific fluid intakes are associated with bladder cancer risk in the study population and that genetic variants of UGT genes could modulate the effects. These results facilitate identification of high-risk individuals and have important implications in bladder cancer prevention.

Bladder cancer is one of the most common genitourinary cancers in the United States, with an estimated 69 250 new incident cases and 14 990 deaths in 2011 (Siegel *et al*, 2011). Established risk factors of bladder cancer include male sex, old age, tobacco smoking, and occupational exposures to aromatic amines (Wu *et al*, 2008).

The role of fluid consumption and its association with the risk of bladder cancer has gained much attention in recent decades (Altieri *et al*, 2003; Ros *et al*, 2011). However, past findings have been inconsistent. For example, pooled data from six case–control studies indicated that total fluid intake was associated with an increased risk in men (Villanueva *et al*, 2006), whereas findings from a large case–control study in seven French hospitals did not support such an association (Geoffroy-Perez and Cordier, 2001). In a Health Professionals Follow-up Study, high fluid intake was associated with reduced risk of bladder cancer (Michaud *et al*, 1999). It has been hypothesised that a high fluid intake might dilute metabolites in the urine and increase the frequency of voiding, thus reducing contact of carcinogens with the bladder epithelium (Pelucchi *et al*, 2006). This hypothesis would suggest that higher levels of fluid intake are beneficial (Bruemmer *et al*, 1997). In contrast, given that fluids may contain substances

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carcinogenic to the bladder, an increase in total fluid quantity might increase the net flow of carcinogens into the bladder and thus increase the risk of cancer (Claude *et al*, 1986).

Potential carcinogenic substances found in specific fluids are metabolised by cytochrome P450 to generate reactive compounds, following a conjugation process by phase II enzymes to generate metabolites for further degradation so that the final product is highly water soluble and easily excreted in bile or urine (Lampe, 2007). Differences in metabolic enzyme activity may modulate the activation and degradation of consumed fluids, resulting in different carcinogenic effects. UDP-glucuronosyltransferases (UGTs), which are membrane-bound conjugating enzymes, catalyse the transformation of hydrophobic substrates to more water-soluble glucuronides to facilitate renal or biliary excretion (King *et al*, 2000; Guillemette, 2003). Target substrates for UGTs cover a wide range of compounds with divergent chemical structures, including dietary by-products, endogenous metabolites, drugs, and occupational and environmental pollutants (Lin *et al*, 2005). Genetic variants have been identified in coding and non-coding regions of UGTs, and the variant genotypes have been reported to be associated with bladder cancer risk (Desai *et al*, 2003; Rothman *et al*, 2010). It has been shown that constitutive expression of UGTs in the normal mucosa could protect organs from carcinogens released in the bladder (Giuliani *et al*, 2005). Tissue-specific loss or decreased expression of UGTs has been reported to be able to experimentally induce bladder tumours in animal models (Giuliani *et al*, 2001; Iida *et al*, 2010).

Considering the role of glucuronidation in the inactivation or elimination of endogenous and exogenous compounds through urine excretion, we hypothesised that genetic variants in UGTs could modulate the effects of fluid intake by interacting with the various types of fluid consumed. To test this hypothesis, we conducted a case–control study to investigate the main effects of total and specific fluid intakes on the risk of bladder cancer, and we further explored their joint effects with selected single-nucleotide polymorphisms (SNPs) of UGT genes.

MATERIALS AND METHODS

Study population. This study started patient recruitment in 1999 and is currently ongoing. The response rates for cases and controls were 92% and 77%, respectively (Wu *et al*, 2007). Bladder cancer cases were enrolled from the University of Texas MD Anderson Cancer Center and Baylor College of Medicine. All patients had histologically confirmed bladder cancer with no prior treatment of chemotherapy or radiotherapy at the time of recruitment. The majority of cases had transitional cell carcinoma, but all histology types were included. There were no restrictions on recruitment regarding age, sex, race, or cancer stage. The control subjects were healthy individuals without cancer history (except non-melanoma skin cancer) and were recruited from the Kelsey-Seybold Clinic, the largest private multispecialty group practice in the Houston metropolitan area, with 18 clinics, more than 325 physicians, and more than 400 000 patients. The control subjects were healthy individuals who visit the Kelsey-Seybold Clinics for annual health checkups. On the day of interview, they came to the clinics for the purpose of participating in this study but not for treating any diseases. Controls were frequency matched to the patients by age (± 5 years), sex, and ethnicity. This study was approved by the Institutional Review Boards of MD Anderson Cancer Center, Kelsey-Seybold Clinic, and Baylor College of Medicine. Written informed consent was obtained from all study subjects. Individuals who never smoked or had smoked less than 100 cigarettes in his or her lifetime were defined as never smoker. Individuals who had quit smoking at least 1 year before diagnosis were defined as former smokers. Individuals who were currently smoking or who had stopped less than 1 year before diagnosis were defined as current smokers. Ever smoker include both former and current smoker. Pack year of smoking was defined as number of cigarettes per day divided by 20 (20 cigarettes per pack) and then multiplied by years of smoking.

Data collection. Trained MD Anderson Cancer Center staff interviewers administered a risk factor questionnaire to all participants. Data collected included demographic characteristics, occupation history, tobacco use history, medical history, lifestyle factors, and family history of cancer. In addition, a food frequency questionnaire (FFQ) was administered to assess usual food intake during the year before diagnosis for the cases and the year before the interview among controls. The FFQ was derived from the Health Habits and History Questionnaire (HHHQ) developed by the National Cancer Institute. The questionnaire included a semiquantitative food frequency list of food and beverage items, ethnic foods commonly consumed in the Houston area, an open-ended section, and dietary behaviours such as dining at restaurants and cooking methods. The validity and reliability of this questionnaire have been documented previously (Block *et al*, 1992). After informed consent was obtained, a blood sample was collected from each participant for molecular analyses.

Calculation of fluid intake. We calculated total and specific fluid intakes using the beverage items in the HHHQ. In the HHHQ, responses regarding the frequency of consumption and amount of consumption each time were recorded. Total fluid intake was expressed as milliliters per day. Specific fluid intake quantities were expressed in servings per day, based on the standard size of glasses or cups according to the particular fluid type. For example, one serving of coffee, tea, water, or total alcoholic beverage is equivalent to one cup (8 fl oz; 240 ml); one serving of beer is equivalent to one glass or one bottle (12 fl oz; 360 ml); one serving of wine is equivalent to one glass (4 fl oz; 120 ml); one serving of liquor is equivalent to one drink (4 fl oz) or one shot (45 ml). Water intake was calculated by adding up the consumption of both tap and bottled water.

Single-nucleotide polymorphism selection and genotyping. Owing to the small number of minority participants in the study populations, we restricted the analysis of SNPs to Caucasians (non-Hispanic whites) in this study. Tagging SNPs were identified from the HapMap database (http://www.hapmap.org) with the following selection criteria: $r^2 \geqslant 0.8$, minor allele frequency $\geqslant 0.05$ in Caucasians, and within 10 kb upstream of the 5′ untranslated region (UTR) and 10 kb downstream of the 3′ UTR of the gene. In addition, we chosed potentially functional SNPs, including coding SNPs and SNPs in UTRs, promoters or splicing sites. Genotyping of selected SNPs followed the workflow of the Illumina Infinium II assay (Illumina, San Diego, CA, USA). A total of 83 SNPs in UGT genes were initially selected, and 8 SNPs were removed due to low-call rate ($<90\%$), departure from Hardy–Weinberg equilibrium ($P<0.01$), or minor allele frequency <0.01. Seventy-five SNPs were included in the final analysis (Supplementary Table 1).

Statistical analysis. Statistical analysis was performed by using STATA 10.0 software (StataCorp, College Station, TX, USA) and the R software (http://www.r-project.org/). All tests were two-sided with the significance level set at 0.05. Distributions of characteristics between cases and controls were tested using the χ^2 test (for categorical variables), Student's *t*-test (for continuous variables with normal distribution), or Kruskal–Wallis nonparametric test (for continuous variables without normal distribution) where appropriate. The multivariate unconditional logistic regression model was used to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs), whereas adjusting for age, sex, ethnicity, energy intake, and smoking status. For total fluid and water

intakes, ORs were calculated using quartile cutoff points in controls. For tea, soft drink, coffee, and alcoholic beverages, the consumption was first categorised into two groups (never drinkers and ever drinkers), and then the subgroup of ever drinkers was further categorised into low-intake and high-intake groups according to the median consumption in the control population. For the main effect of single SNP analysis, we tested three different genetic models: dominant model, recessive model, and additive model. The best-fitting model was the one with the smallest *P*-value among the three models. If the counts for the homozygous variant genotype were less than 5% in both cases and controls, only the dominant model that had the highest statistical power was considered. To control for false positives resulting from multiple comparisons, we adjusted the *P*-values of single SNP by using the *q*-value module in the R software. The analysis of SNPs was restricted to Caucasians only to address population stratification in genetic association studies. Interactions between variables were included in the multivariate logistic regression model as cross-product terms, and the significance was assessed using the likelihood ratio test.

RESULTS

As shown in Table 1, 1007 cases (784 men, 223 women) and 1299 controls (1013 men, 286 women) were included in the study. The majority of the study participants were white (91.46% for cases and 90.84% for controls, $P = 0.595$). The distributions of sex, age, and ethnicity were comparable between cases and controls as a result of frequency matching. The proportion of current smokers was higher in cases than in controls (24.93% *vs* 8.39%, $P < 0.001$). Smokers in the case group also had higher number of pack-years of smoking than smokers in the control group (median: 36.0 *vs* 22.5, $P < 0.001$). Energy intake was significantly higher in cases than in controls (2258 *vs* 1968 kcal per day, $P < 0.001$; Table 1).

Table 1. Characteristics of cases and controls

	Control ($n = 1299$)	Case ($n = 1007$)	
Characteristic	***n* (%)**	***n* (%)**	***P*-value**
Sex			
Men	1013 (77.98)	784 (77.86)	0.941[a]
Women	286 (22.02)	223 (22.14)	
Age (years)			
Mean ± s.d.	64.20 ± 11.37	64.64 ± 11.12	0.352[b]
Ethnicity			
White	1180 (90.84)	921 (91.46)	0.595[a]
Hispanic	49 (3.77)	40 (3.97)	
Black	60 (4.62)	36 (3.57)	
Other	10 (0.77)	10 (0.99)	
Smoking status			
Never	594 (45.73)	287 (28.50)	**<0.001**[a]
Former	596 (45.88)	469 (46.57)	
Current	109 (8.39)	251 (24.93)	
Smoking pack-years			
Median (range)	22.5 (0.05–165)	36.0 (0.10–176)	**<0.001**[c]
Energy intake (kcal per day)			
Median (range)	1968 (516–9502)	2258 (381–6988)	**<0.001**[c]

[a] χ^2 test.
[b] Student's *t*-test.
[c] Kruskal–Wallis test.

The median total fluid intake was higher in cases than in controls (2423 *vs* 2215 ml per day, $P < 0.001$). For water, tea, soft drinks, coffee, and total alcoholic beverages, the median (95% CI) servings per day were 3.50, 0.68, 0.71, 2.00, and 0.55 among cases and 3.50, 0.71, 0.71, 2.00, and 0.39 among controls, respectively (Supplementary Table 2).

After adjustment for potential confounders, the highest quartile of fluid intake (⩾2789 ml per day) was associated with an increased risk of bladder cancer, with an OR of 1.41 (95% CI = 1.10–1.81), compared with the lowest quartile (<1696 ml per day; Table 2). No significant association was found between overall water consumption (tap and bottle water combined) and the risk of bladder cancer. Increased tea consumption conferred significantly reduced risks, with ORs of 0.74 (95% CI = 0.59–0.92) for <0.71 serving per day and 0.65 (95% CI = 0.53–0.81) for ⩾0.71 serving per day, with a significant dose-response trend (*P* for trend < 0.001). When stratified by type of tea, the protective effects were observed for black, green, and herbal teas but not for decaffeinated tea consumption. For soft drink consumption, compared with never drinkers, low (<0.70 serving per day) and high (⩾0.71 serving per day) consumption of soft drinks conferred 26% (OR = 1.26, 95% CI = 1.00–1.60) and 34% (OR = 1.34, 95% CI = 1.05–1.70) increased risks of bladder cancer. However, these increased risks were observed only with regular soft drink consumption and not with diet soft drink consumption. Overall, coffee consumption was not significantly associated with bladder cancer risk. However, an increased risk was found for consuming decaffeinated coffee, with ORs of 1.75 (95% CI = 1.28–2.41) for <1 serving per day and 1.37 (95% CI = 1.09–1.73) for ⩾1 serving per day (*P* for trend = 0.001). This increased risk was not observed in regular coffee drinkers. Consumption of alcoholic beverages was inversely associated with bladder cancer risk, with ORs 0.59 (95% CI = 0.48–0.74) for <0.39 serving per day and 0.77 (95% CI = 0.62–0.95) for ⩾0.39 serving per day. The inverse association was observed only in wine and liquor drinkers and not in beer drinkers. For example, compared with never drinkers, wine consumption (⩾0.14 serving/day) conferred 41% reduction in bladder cancer risk (OR = 0.59, 95% CI = 0.48–0.73).

To explore potential association between smoking and beverage choice, we performed an analysis of smoking status and beverage drinking habits in controls. Results showed that there was significant difference in total and some specific fluid intake by smoking status (Supplementary Table 3). Specifically, smokers tended to have high consumption of total fluid, coffee of all types, regular coffee, total alcoholic beverages, beer, and liquor. In contrast, never smokers were more likely to have high consumption of tea, especially green tea and other herbal tea.

We further performed a stratified analysis by smoking status. Results showed that the inverse association between bladder cancer and all types of tea and specific tea, all types of alcoholic beverages, and liquor was only significant in ever smokers (Supplementary Table 4). Similarly, the increased risk associated with all types of soft drinks and regular soft drinks was significant in ever smokers but not in never smokers (Supplementary Table 4). However, there was no significant interaction between smoking and fluid intake of any kind.

A total of 1501 subjects (718 cases, 783 controls) with genotype data available were included in the SNP analysis. We did an analysis comparing demographic and fluid intake differences between all subjects and subjects with genotype data available but found no differences (data not shown). Eighteen SNPs in the UGT gene family were individually associated with bladder cancer (Table 3). Of these 18 SNPs, 16 are located in the genes of the UGT1 family and 2 in the genes of the UGT2 family. After

Table 2. Fluid intake and the risk of bladder cancer

Fluid intake	Control/case	OR (95% CI)[a]	P
Total fluid intake (ml/day)			
<1696	324/218	1	
1696–2215	325/215	0.92 (0.71–1.18)	0.517
2215–2789	324/191	0.81 (0.62–1.05)	0.109
≥2789	325/382	1.41 (1.10–1.81)	0.007
P for trend			0.01
Water (serving/day)			
<2	217/202	1	
2–3.4	300/217	0.84 (0.64–1.11)	0.218
3.5–4.9	329/204	0.78 (0.60–1.03)	0.078
≥5	452/383	1.02 (0.80–1.31)	0.856
P for trend			0.565
All types of tea (serving/day)			
Never	312/328	1	
0.1–0.70	472/342	0.74 (0.59–0.92)	0.007
0.71+	515/337	0.65 (0.53–0.81)	<0.001
P for trend			<0.001
Decaffeinated tea (serving/day)			
Never	1155/877	1	
0.1–0.56	66/61	1.38 (0.95–2.00)	0.092
0.57+	78/69	1.35 (0.96–1.92)	0.088
P for trend			**0.031**
Black tea (serving/day)			
Never	515/492	1	
0.1–0.56	381/250	0.71 (0.57–0.88)	0.001
0.57+	403/265	0.67 (0.54–0.83)	<0.001
P for trend			<0.001
Green tea (serving/day)			
Never	972/828	1	
0.1–0.13	133/88	0.82 (0.61–1.11)	0.197
0.14+	194/91	0.60 (0.45–0.79)	<0.001
P for trend			<0.001
Other herbal tea (serving/day)			
Never	1120/937	1	
0.1–0.13	82/26	0.44 (0.27–0.69)	<0.001
0.14+	97/44	0.60 (0.41–0.88)	0.009
P for trend			<0.001
All types of soft drink (serving/day)			
Never	286/187	1	
0.1–0.70	506/393	1.26 (1.00–1.60)	0.055
0.71+	507/427	1.34 (1.05–1.70)	0.018
P for trend			0.025
Diet soft drink (serving/day)			
Never	705/589	1	
0.1–0.85	294/197	0.96 (0.77–1.19)	0.702
0.86+	300/221	1.06 (0.85–1.32)	0.62
P for trend			0.713
Regular soft drink (serving/day)			
Never	758/505	1	
0.1–0.34	270/232	1.28 (1.03–1.60)	0.025
0.35+	271/270	1.27 (1.02–1.58)	0.032
P for trend			0.014
All types of coffee (serving/day)			
Never	259/155	1	
0.1–1.9	375/271	1.13 (0.87–1.47)	0.372
2+	665/581	1.14 (0.90–1.46)	0.283
P for trend			0.336
Decaffeinated coffee (serving/day)			
Never	1006/717	1	
0.1–0.9	89/94	1.75 (1.28–2.41)	0.001
1+	203/196	1.37 (1.09–1.73)	0.007
P for trend			0.001
Regular coffee (serving/day)			
Never	389/288	1	
0.1–1.9	332/235	0.91 (0.72–1.15)	0.437
2+	577/484	0.92 (0.74–1.13)	0.401
P for trend			0.426
Total alcoholic beverage (serving/day)			
Never	368/366	1	
0.1–0.38	465/265	0.59 (0.48–0.74)	<0.001
0.39+	466/376	0.77 (0.62–0.95)	0.016
P for trend			0.021
Wine (serving/day)			
Never	574/586	1	
0.1–0.13	329/205	0.66 (0.53–0.82)	<0.001
0.14+	396/216	0.59 (0.48–0.73)	<0.001
P for trend			<0.001
Beer (serving/day)			
Never	727/563	1	
0.1–0.13	256/183	0.96 (0.76–1.21)	0.749
0.14+	316/261	0.99 (0.80–1.24)	0.961
P for trend			0.917
Liquor (serving/day)			
Never	748/651	1	
0.1–0.06	274/149	0.66 (0.52–0.83)	<0.001
0.07+	277/207	0.77 (0.61–0.96)	0.019
P for trend			0.003

Abbreviations: CI = confidence interval; OR = odds ratio.
[a]Adjusting for age, sex, ethnicity, energy intake, and smoking.

adjustment for multiple comparisons, 11 SNPs remained significant ($q<0.05$), with the most significant one being rs7571337, which conferred 29% reduced risks for variant genotype carriers (OR = 0.71, 95% CI = 0.56–0.90).

We next stratified the association between total and specific fluid intakes by rs7571337 genotypes. As shown in Table 4, the increased risks conferred by total fluid intake (OR = 2.02 for total fluid intake > = 2789 ml per day) and soft drink (OR = 2.01 for soft drinks 0.1–1.9 serving per day; OR = 1.86 for soft drinks 0.71 or more servings per day) and coffee consumption (OR = 2.04 for 0.1–1.9 servings per day; OR = 2.26 for 2 or more servings per day) were significant only among rs7571337 AA genotype carriers, whereas the inverse association of tea (OR = 0.56 for 0.1–0.7 servings per day; OR = 0.62 for 0.71 or more servings per day) and alcoholic beverage consumption (OR = 0.72 for 0.1–0.38 servings per day) was observed only in AG/GG carriers.

DISCUSSION

This is the first study evaluating fluid consumption and its joint effects with genetic variants in UGT family genes. Our results suggest that total fluid intake was associated with an increased risk and that when stratified by specific fluid type, high intake of regular soft drinks increased the risk, whereas high intakes of regular tea, wine, and liquor decreased the risk. Moreover, we found the effects of fluid intake could be modified by genetic polymorphisms of UGT genes.

Previous epidemiological studies have evaluated the risks of bladder cancer in association to the fluid intake. A study in western New York reported that total fluid consumption was a risk factor for bladder cancer when a number of potential confounding risk factors were controlled for (OR = 3.74; 95% CI = 2.55–5.47) the highest quartile of fluid consumption (Vena *et al*, 1993). It is hypothesised that moderate fluid intake might dilute metabolites in the urine and increase the frequency of voiding, thus reducing contact of carcinogens with the bladder epithelium (Bruemmer *et al*, 1997; Pelucchi *et al*, 2006). However, given that fluids may contain substances carcinogenic to the bladder, an increase in total fluid quantity might increase the net flow of carcinogens into the bladder and thus increase the risk of cancer (Claude *et al*, 1986). Our results are consistent with this hypothesis. However, total fluid consumption has been associated with a decreased risk in some studies (Michaud *et al*, 1999, 2007) or with no association in others (Geoffroy-Perez and Cordier, 2001; Brinkman and Zeegers, 2008; Jiang *et al*, 2008; Ros *et al*, 2011). The inconsistent results might be due to the lack of consideration of specific types of fluid. Also, studies varied in size and the calculation of fluid intake also varied by studies, which makes comparison between studies difficult. Moreover, previous studies did not consider genetic variations and differences in host metabolic enzyme activity could also partly be responsible for the inconsistent results.

UGTs are the major class of metabolic enzymes that catalyse phase II reactions (Iyanagi, 2007). Other genes that are involved in the detoxification of carcinogens include glutathione *S*-transferases, sulfotransferase and *N*-acetyltransferase. Potential chemical existing in the beverages first get activated by phase I drug metabolising enzymes, and then be deactivated by phase II drug metabolising enzymes like UGTs. A full picture of the lipophilic process of the chemicals in the various fluids should be discussed in the context of both phase I and phase II metabolic phases. In the liver and gastrointestinal tract, UGTs are predominantly expressed, but the expression of human UGTs varies widely between individuals (Mackenzie *et al*, 2005). Mediated by the UGTs of the endoplasmic reticulum and nuclear envelope, a myriad of lipophilic chemicals are rendered water soluble, and this process has a critical role in the detoxification of exogenous and endogenous compounds (Iyanagi, 2007). In light of the association of genetic predisposition and fluid intake to cancer risk, we stratified the analysis of total and specific fluid intakes by genetic variants in the UGTs to further elucidate their joint effects. Our findings supported the hypothesis that effects of fluid intake could be modified by genetic polymorphisms of UGT genes individually and cumulatively. However, the functions of the significant SNPs that we found in this study were unclear. More in-depth molecular studies are needed to confirm the functional significance of the SNPs. The most significant SNP, rs7571337, is located in the intron region of *UGT1A8* (UDP glucuronosyltransferase 1 family, polypeptide A8). Whether this SNP can alter the expression of the *UGT1A8* gene or links to other functional loci needs to be verified.

In addition to total fluid intake, we also evaluated specific fluid items, including water, tea, soft drinks, coffee, and alcoholic beverages. A Health Professionals Follow-up Study reported that the consumption of water contributed to a lower risk (relative risk, 0.49 (95% CI: 0.28–0.86) for $\geqslant$1440 *vs* $<$240 ml per day; Michaud *et al*, 1999). A case–control study of bladder cancer in Spain also found a significant inverse association for water intake (OR = 0.47; 95% CI = 0.33–0.66; for $>$1399 *vs* $<$400 ml per day; Michaud *et al*, 2007). Inconsistent with these former findings (Michaud *et al*, 1999, 2007), we found no significant association between overall water consumption and bladder cancer. This inconsistency in findings may be due to differences in exposures to disinfection by-products and other water contaminants that can vary substantially by study population (Michaud *et al*, 2007). Drinking tap water containing chlorine and chlorination by-products has been demonstrated to increase the risk of developing bladder cancer in several studies (Cantor *et al*, 1987; Villanueva *et al*, 2004). Unfortunately, our study did not collect information on the source of drinking water, so we were not able to compare the effects of drinking tap *vs* non-tap water on bladder cancer risk.

Our results suggest a protective effect for tea drinking. Tea is one of the most common beverages consumed worldwide (Boehm *et al*, 2009). It contains several polyphenolic components with antioxidant properties. Extracts of tea have been shown to inhibit the formation and development of tumours in animal models (Yang *et al*, 2009). Considerable evidence from epidemiological studies has indicated the potential use of tea for cancer prevention (Bushman, 1998; Boehm *et al*, 2009; Yang *et al*, 2009).

Our results also suggested that high consumption of soft drinks was associated with increased risk, and this association was found for drinkers of regular soft drinks but not drinkers of diet soft drinks. Ingestion of soft drinks tends to cause a rapid increase in blood sugar and insulin relative to many other beverages and foods (Odegaard *et al*, 2010). Soft drinks and other sweetened beverages may contribute to the risk of obesity and diabetes (Albanes, 1987; Mueller *et al*, 2010; Odegaard *et al*, 2010). However, the consumption of added sugar or of sugar-sweetened foods and beverages in the risk of human cancers is still controversial. We recently reported high caloric intake was associated with bladder cancer (Lin *et al*, 2010).

The role of coffee in bladder cancer has been examined in several epidemiological studies, with some conflicting results (Pelucchi *et al*, 2008; Pelucchi and La Vecchia, 2009). A study by a Spanish group reported no significant association between coffee consumption and bladder cancer (Villanueva *et al*, 2009). A prospective cohort study in Japan found that coffee was positively associated with bladder cancer risk in men, but without statistical significance (Kurahashi *et al*, 2009). However, results from the Netherlands Cohort Study suggested a probable inverse association between coffee consumption and bladder cancer risk in women (Zeegers *et al*, 2001). Our results are consistent with previously published epidemiological studies that suggest a null or slightly positive association between coffee and bladder cancer. Coffee is a complex mixture of chemicals, and a large array of compounds found in coffee could potentially alter cancer risk through several biological mechanisms (Higdon and Frei, 2006; Nkondjock, 2009). Animal studies have shown the effect of caffeine to both stimulate and suppress tumours, depending upon the species and the phase of administration (Nkondjock, 2009). In this study, an increased risk for bladder cancer was found only for decaffeinated coffee rather than regular coffee. Whether this difference can be attributed to the role of caffeine or other chemicals in these two types of coffee needs further study. In addition, a potential misclassification of coffee types may be another explanation. For example, former users of caffeinated coffee among the cases may have switched to decaffeinated coffee as part of a healthy lifestyle, resulting in the overestimation of risk.

Findings from our study were consistent with former reports that alcoholic beverage consumption was inversely related to bladder cancer risk (Jiang *et al*, 2007). This protective effect was

Table 3. Association between genetic polymorphisms of UGTs and bladder cancer risk

			Genotype			MAF	Model		
SNP	Region	Case/Control	WW	WV	VV		Model	OR (95% CI)[a]	*P*-value
rs7571337	Chr2:234231157	Case	215	336	163	0.46	Dom	0.71 (0.56–0.90)	0.005
		Control	189	391	203	0.51	Rec	0.84 (0.66–1.08)	0.169
							Add	0.82 (0.71–0.95)	0.009
rs17864684	Chr2:234244102	Case	534	165	19	0.14	Dom	0.72 (0.57–0.90)	0.005
		Control	529	227	27	0.18	Rec	0.81 (0.44–1.49)	0.496
							Add	0.76 (0.62–0.93)	0.009
rs4233633	Chr2:234284676	Case	581	123	14	0.11	Dom	0.72 (0.55–0.93)	0.012
		Control	598	177	6	0.12	Rec	0.42 (0.91–6.46)	0.077
							Add	0.80 (0.63–1.02)	0.068
rs2736520	Chr4:70370761	Case	511	189	18	0.16	Dom	1.36 (1.07–1.73)	0.012
		Control	593	171	19	0.13	Rec	1.09 (0.55–2.13)	0.812
							Add	1.27(1.03–1.57)	0.023
rs3822179	Chr4:70390784	Case	614	98	6	0.08	Dom	0.70 (0.53–0.93)	0.015
		Control	633	139	11	0.10	Rec	0.68 (0.24–1.91)	0.461
							Add	0.73 (0.56–0.94)	0.016
rs4148326	Chr2:234338201	Case	205	358	155	0.47	Dom	1.33 (1.06–1.67)	0.015
		Control	270	361	152	0.42	Rec	1.11 (0.86–1.44)	0.426
							Add	1.17 (1.01–1.35	0.041
rs1604144	Chr2:234270574	Case	390	276	52	0.26	Dom	0.77 (0.63–0.96)	0.017
		Control	386	324	73	0.30	Rec	0.77 (0.52–1.13)	0.177
							Add	0.82 (0.69–0.96)	0.015
rs17868322	Chr2:234245233	Case	653	63	2	0.05	Dom	1.63 (1.09–2.44)	0.019
		Control	734	44	2	0.03	Rec	0.89 (0.12–6.74)	0.906
							Add	1.55 (1.05–2.28)	0.027
rs2602374	Chr2:234233703	Case	357	288	73	0.30	Dom	1.07 (0.87–1.32)	0.527
		Control	408	319	56	0.28	Rec	1.57 (1.07–2.29)	0.020
							Add	1.13 (0.96–1.34)	0.131
rs17854828	Chr2:234210600	Case	543	157	18	0.13	Dom	0.76 (0.60–0.96)	0.022
		Control	553	205	25	0.16	Rec	0.84 (0.45–1.57)	0.583
							Add	0.80 (0.65–0.98)	0.032
rs4148328	Chr2:234342398	Case	307	317	94	0.35	Dom	0.84 (0.67–1.03)	0.100
		Control	299	361	123	0.39	Rec	0.71 (0.52–0.96)	0.028
							Add	0.84 (0.72–0.98)	0.023
rs2741042	Chr2:234230656	Case	337	297	84	0.32	Dom	1.12 (0.91–1.38)	0.286
		Control	396	320	67	0.29	Rec	1.49 (1.05–2.12)	0.026
							Add	1.16 (0.99–1.36)	0.069
rs1113193	Chr2:234233876	Case	413	259	45	0.24	Dom	0.79 (0.64–0.98)	0.028
		Control	410	319	54	0.27	Rec	0.94 (0.61–1.43)	0.764
							Add	0.85 (0.72–1.01)	0.060
rs1104892	Chr2:234285011	Case	179	369	169	0.49	Dom	1.30 (1.03–1.64)	0.030
		Control	241	375	167	0.45	Rec	1.12 (0.87–1.44)	0.395
							Add	1.15 (0.99–1.34)	0.061
rs2741044	Chr2:234244107	Case	338	293	75	0.31	Dom	1.15 (0.93–1.43)	0.189
		Control	403	310	60	0.28	Rec	1.49 (1.03–2.16)	0.034
							Add	1.18 (1.00–1.38)	0.051
rs2741045	Chr2:234244879	Case	337	306	75	0.32	Dom	1.16 (0.94–1.43)	0.163
		Control	403	320	60	0.28	Rec	1.49 (1.03–2.15)	0.036
							Add	1.18 (1.00–1.39)	0.045
rs1105880	Chr2:234266704	Case	292	327	99	0.37	Dom	1.19 (0.96–1.48)	0.106
		Control	356	342	85	0.33	Rec	1.36 (0.98–1.87)	0.064
							Add	1.18 (1.01–1.38)	0.037
rs6759892	Chr2:234266408	Case	233	342	143	0.44	Dom	1.20 (0.96–1.50)	0.106
		Control	289	369	125	0.40	Rec	1.29 (0.98–1.70)	0.070
							Add	1.17 (1.01–1.36)	0.038

Abbreviations: Add = additive model; CI = confidence interval; Dom = dominant model; MAF = minor allele frequency; OR = odds ratio; Rec = recessive model; SNP = single-nucleotide polymorphism; UGT = UDP-glucuronosyltransferases; VV = homozygous variant genotype; WV = heterozygous genotype; WW = wild-type genotype.
[a]Adjusting for age, sex, ethnicity, and smoking.

Table 4. Association between fluid intake and the risk of bladder cancer stratified by rs7571337 genotype

	AA				AG + GG			
Variable	**Control**	**Case**	**OR (95% CI)[a]**	***P*-value**	**Control**	**Case**	**OR (95% CI)[a]**	***P*-value**
Total fluid intake (ml per day)								
<1696	40	37	1		126	102	1	
1696–2215	52	51	0.98(0.53–1.81)	0.955	143	102	0.84(0.57–1.22)	0.358
2215–2789	53	36	0.73(0.39–1.37)	0.329	150	116	0.84(0.58–1.22)	0.368
⩾2789	44	91	2.02(1.08–3.78)	**0.028**	175	179	1.03(0.71–1.48)	0.893
P for trend				**0.039**				0.776
Water (serving per day)								
<2	31	48	1		105	103	1	
2–3.4	45	41	0.56(0.30–1.08)	0.083	139	119	0.99(0.67–1.46)	0.971
3.5–4.9	43	40	0.62(0.32–1.19)	0.149	139	102	0.89(0.60–1.32)	0.547
⩾5	70	86	0.80(0.45–1.42)	0.438	211	175	0.96(0.67–1.37)	0.809
P for trend				0.814				0.73
Tea (serving per day)								
Never	47	59	1		135	174	1	
0.1–0.70	81	82	0.89(0.53–1.49)	0.666	230	161	0.56(0.41–0.77)	<0.001
0.71+	61	74	1.00(0.59–1.71)	0.999	229	164	0.62(0.45–0.84)	0.003
P for trend				0.960				0.004
Soft drinks (serving per day)								
Never	44	30	1		113	108	1	
0.1–0.70	68	95	2.01(1.13–3.59)	**0.018**	230	184	0.86(0.61–1.22)	0.403
0.71+	77	90	1.86(1.03–3.36)	**0.039**	251	207	0.88(0.62–1.24)	0.452
P for trend				0.081				0.517
Coffee (serving per day)								
Never	43	24	1		106	73	1	
0.1–1.9	52	57	2.04(1.07–3.89)	**0.030**	165	127	1.08(0.72–1.60)	0.716
2+	94	134	2.26(1.26–4.07)	**0.007**	323	299	1.06(0.74–1.52)	0.737
P for trend				**0.013**				0.796
Total alcoholic beverages (serving per day)								
Never	52	72	1		176	173	1	
0.1–0.38	63	55	0.64(0.38–1.09)	0.099	200	136	0.72(0.53–1.00)	0.048
0.39+	74	88	0.82(0.50–1.36)	0.448	218	190	0.89(0.65–1.21)	0.448
P for trend				0.514				0.490

Abbreviations: CI = confidence interval; OR = odds ratio.
[a]Adjusting for age, sex, ethnicity, energy intake, and smoking

observed in both wine and liquor drinkers, but not for beer consumers. Wine is a moderately alcoholic drink made by fermentation of juice extracted from grapes. Wine contains antioxidant phenolic substances, including piceatannol. Experimental studies showed that piceatannol inhibited the proliferation of human bladder cancer cells by blocking cell cycle progression in the G0/G1 phase and inducing apoptosis, resulting in potential anti-carcinogenesis effects (Kuo and Hsu, 2008). In addition to wine, liquor also showed a protective effect in our study, which might be attributed to the role of alcohol. Previous reports documented the diuretic properties of alcohol in both experimental animals and humans, with alcohol consumption increasing urine flow, which may have a role in alcohol-mediated bladder cancer protection by decreasing the time that the bladder is exposed to carcinogens in the urine (Jiang *et al*, 2007).

In this study, cases and controls were retrospectively interviewed about their fluid consumption. Bias could potentially be introduced if the cases changed their diet habits before diagnosis due to the disease. To reduce this bias, cases were asked about their usual fluid intake a year before diagnosis. However, given that carcinogenesis is a long-term process, consumption of fluid one year before cancer diagnosis may not serve as an ideal measure of cumulative exposure. Further, it may be challenging to quantify fluid intake. Although there are better methods to quantify fluid intake than FFQ, in epidemiologic studies with large number of participants, FFQ is regarded as an efficient method to quantify the relative amount of intake, which determines the relative risk groups. Finally, although we adjusted for potential confounders such as age, sex, ethnicity, energy intake, and smoking in this study, we cannot exclude the possibility that some unmeasured confounders accounted for the associations found in this study.

In conclusion, results from the present study suggest that total fluid intake is associated with an increased risk of bladder cancer. Drinking tea, wine, and liquor confers decreased risks for bladder cancer, whereas regular soft drinks and decaffeinated coffee consumption may be possible risk factors. Results from this study

suggest that genetic variants of UGT genes modulate an individual's susceptibility by interacting with the specific type of consumed fluids.

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CONFLICT OF INTEREST

The authors declare no conflict of interests.

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