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Flavonoid and lignan intake in relation to bladder cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) study

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Background: There is growing evidence of the protective role of dietary intake of flavonoids and lignans on cancer, but the association with bladder cancer has not been thoroughly investigated in epidemiological studies. We evaluated the association between dietary intakes of total and subclasses of flavonoids and lignans and risk of bladder cancer and its main morphological type, urothelial cell carcinoma (UCC), within the European Prospective Investigation into Cancer and Nutrition (EPIC) study.

Methods: A cohort of 477 312 men and women mostly aged 35–70 years, were recruited in 10 European countries. At baseline, dietary flavonoid and lignan intakes were estimated using centre-specific validated questionnaires and a food composition database based on the Phenol-Explorer, the UK Food Standards Agency and the US Department of Agriculture databases.

Results: During an average of 11 years of follow-up, 1575 new cases of primary bladder cancer were identified, of which 1425 were UCC (classified into aggressive ($n=430$) and non-aggressive ($n=413$) UCC). No association was found between total flavonoid intake and bladder cancer risk. Among flavonoid subclasses, significant inverse associations with bladder cancer risk were found for intakes of flavonol (hazard ratio comparing fifth with first quintile ($HR_{Q5–Q1}$) 0.74, 95% confidence interval (CI): 0.61–0.91; P-trend $=0.009$) and lignans ($HR_{Q5–Q1}$ 0.78, 95% CI: 0.62–0.96; P-trend $=0.046$). Similar results were observed for overall UCC and aggressive UCC, but not for non-aggressive UCC.

Conclusions: Our study suggests an inverse association between the dietary intakes of flavonols and lignans and risk of bladder cancer, particularly aggressive UCC.

Bladder cancer is the sixth most common cancer type and the seventh most common cause of death from cancer in Europe overall, although certain populations are highly affected (Ferlay *et al*, 2010). Indeed, men are about three times more likely to develop bladder cancer compared with women (Ferlay *et al*, 2010). Moreover, it is predominantly a disease of high-income countries and overall rates have remained relatively stable over the last decades (Burger *et al*, 2013).

In 2007, a comprehensive review by the World Cancer Research Fund and the American Institute for Cancer Research concluded that established risk factors for bladder cancer include tobacco consumption, infection with *Schistosoma haematobium*, and both occupational and environmental exposures to carcinogens such as aromatic amines and polycyclic aromatic hydrocarbons and arsenic in drinking water. In contrast they showed that food, nutrition and physical activity only had modest effects in the development of bladder cancer (World Research Cancer Fund and American Institute for Cancer Research, 2007). Since then, investigations of the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort have found that fruit and vegetable intake measured from dietary questionnaires was not clearly related to bladder cancer (Buchner *et al*, 2009; Ros *et al*, 2012), although higher plasma carotenoids concentrations were associated with lower incidence of bladder cancer (Ros *et al*, 2010); suggesting that specific compounds in fruit and vegetables may have protective associations with bladder cancer risk. In addition, a recent study in the multiethnic cohort has suggested that intake of fruit and vegetables and some related micronutrients such as vitamins A, C, E and carotenoids were inversely associated with bladder cancer risk only in women (Park *et al*, 2013).

One group of bioactive compounds in fruit and vegetables of growing interest for chronic disease prevention is polyphenols (basically flavonoids, phenolic acids and lignans), which have been shown to have antioxidant, anti-inflammatory and anti-carcinogenic effects in animals and *in vitro* studies (Yao *et al*, 2004; Xiao *et al*, 2011). The biological activity of flavonoids and lignans in the prevention of bladder cancer is plausible considering that most of the flavonoid and lignan metabolites are excreted through urine, exposing the bladder lining to these metabolites (Manach *et al*, 2005).

To the best of our knowledge, only the Iowa Women's Health Study prospectively assessed the relationship between flavan-3-ol monomer intake (a flavonoid subclass) and bladder cancer risk, and found no association (Arts *et al*, 2002). Moreover, in a Spanish case–control study, no associations were observed with some individual flavonols and flavones (Garcia *et al*, 1999). Further epidemiological studies in other large populations (including men) and the assessment of the effect of the other flavonoid subclasses are needed. Therefore, the aim of this study was to investigate the association between the dietary intake of both total and subclasses of flavonoids and lignans and bladder cancer risk in the EPIC study, a large cohort with a high variability in the intake of these compounds (Zamora-Ros *et al*, 2012, 2013).

MATERIALS AND METHODS

Study design. The EPIC is an on-going multicentre cohort study designed to examine the association between diet, lifestyle and environmental factors and cancer. The full rationale, methods and design have been described previously (Riboli and Kaaks, 1997; Riboli *et al*, 2002). Briefly, the EPIC study involves more than half a million men and women from 23 centres in 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom). Participants, mostly

aged between 35 and 70 years, were recruited from primarily the general population during the period 1991–2000 (Riboli and Kaaks, 1997; Riboli *et al*, 2002). All participants gave written informed consent, and the study was approved by the local ethics committees in the participating countries and the ethical review board of the International Agency for Research on Cancer (IARC).

Case ascertainment and follow-up. Follow-up for end point status was mostly based on population cancer registries, except for France, Germany and Greece, where a combination of methods including health insurance records, cancer and pathology hospital registries, and active follow-up were used. Mortality data were also collected from registries at the regional or national level. The date of the last complete follow-up (recorded in a central database at IARC) ranged from December 2004 to June 2010, depending on the centre.

Bladder cancer cases were coded as C67 following the third edition of the International Classification of Diseases for Oncology (ICD-O-3). Bladder cancer cases with morphology codes 8980 (carcinosarcoma), 9590 (malignant lymphoma), 9671 (malignant lymphoma, lymphoplasmacytic) and tumours with benign behaviours were censored at date of diagnosis. The analyses were also done separately for the urothelial cell carcinomas (UCCs), including urothelial cell papillomas and carcinomas (morphology codes 812–813). The UCCs make up >90% of bladder tumours (Allen *et al*, 2013). The UCC cases were separated into relatively aggressive (high risk of progression) and non-aggressive (low risk of progression) (Kiemeney *et al*, 2008), as described previously (Ros *et al*, 2012). Briefly, aggressive UCC cases were defined as stage T1 and higher or carcinoma *in situ* (CIS) or World Health Organization (WHO) grade 3, whereas non-aggressive UCC cases were defined as: stage Ta grade 1 or stage Ta grade 2. Tumour aggressiveness was only classified for UCC cases diagnosed up until 2007, since these have been individually validated by pathology reports, and the remaining tumours were censored at date of diagnosis for stratified analyses.

Participants were excluded from the analyses if they had an extreme energy intake and/or expenditure (participant in the top or the bottom 1% of the distribution of the ratio of total energy intake to energy requirement) ($n=9600$) or if information on dietary intake and lifestyle was incomplete ($n=6253$). Furthermore, 28 289 participants were excluded because they had a prevalent cancer at any site at baseline or were lost to follow-up. In this present analysis, 477 312 subjects were included.

Dietary and lifestyle assessment. At recruitment, participant's dietary intake in the previous year was estimated using validated and centre-specific questionnaires (Margetts and Pietinen, 1997; Riboli *et al*, 2002). Dietary questionnaires in most of the centres were quantitative, estimating portion sizes systematically. In Denmark, Norway, Umeå (Sweden) and Naples (Italy), semiquantitative food-frequency questionnaires were administered. In Malmö (Sweden), a modified diet history method was used, combining information from a 7-day diet record, a semiquantitative questionnaire and a 1-h dietary interview. Energy (kcal day^{-1}) and ethanol (g day^{-1}) intakes were estimated using the EPIC Nutrient Database (Slimani *et al*, 2007). Lifestyle questionnaires included questions on education, medical history, lifetime history of consumption of tobacco and physical activity (Riboli *et al*, 2002; Wareham *et al*, 2003). Height and weight at baseline were measured in most of the centres, except for Oxford (UK), France and Norway where anthropometric measures at baseline were self-reported. BMI was calculated as weight in kilograms divided by squared height in metres (kg m^{-2}).

Dietary intake of total and subclasses of flavonoids (flavanols (including flavan-3-ol monomers, proanthocyanidins, theaflavins), anthocyanidins, flavonols, flavanones, flavones, and isoflavones) and total lignans were estimated using our own database (Zamora-Ros *et al*, 2012, 2013), which combines food composition data from the USDA databases (U.S.Departament of Agriculture, 2004, 2007, 2008), Phenol-Explorer (Neveu *et al*, 2010) and the UK Food Standards Agency database (Ward *et al*, 2010). Moreover, our food composition database was expanded by using retention factors (except for isoflavones and lignans) (Crozier *et al*, 1997; U.S.Departament of Agriculture, 2008), developing recipes, and estimating missing values based on similar foods (by botanical family and plant part). Data on flavonoids and lignans are expressed as aglycone equivalents, after conversing flavonoid glycosides into aglycone contents using their respective molecular weights. The final database contains 1877 food items (10% have missing values) and includes raw foods, cooked foods and recipes.

Statistical analysis. Flavonoid and lignan intake was assessed by the mean and its s.d., as well as the median and the 5th and 95th centiles (P5th, P95th) because the data were skewed to the right. The distribution of the population's main characteristics according to quintiles of total flavonoid intakes were examined using two-sided χ^2 and Kruskal–Wallis tests, as appropriate. The relationships between dietary intakes of flavonoids and lignans and bladder cancer risk were assessed by estimating the hazard ratio (HR) and its 95% confidence interval (CI) in Cox regression models. Tests and graphs based on Schoenfeld residuals were used to assess the proportional hazards assumption, which was satisfied. Total and subclasses of flavonoids and lignans were categorised using cohort-wide quintiles. Tests for linear trend were performed by assigning the medians of each quintile as scores. Intakes were also analysed continuously after a $\log_2$ transformation that indicates a reduction of bladder cancer risk for doubling flavonoid and lignan intakes. Hazard ratios were estimated using the following modelling strategy; age was used as the underlying time scale, with entry time defined as the participant's age at baseline and exit time as age at cancer diagnosis (for cases) or censoring (for at-risk participants), which was age at death or end of follow-up. Crude models were stratified by centre, sex and age at baseline (1-year intervals). Multivariable model 1 was additionally adjusted for total energy intake (kcal day^{-1}, continuous variable) and smoking status and intensity (never, former quit <11 years, former quit 11–20 years, former quit >20 years, current <15 cigarettes day^{-1}, current 15–25 cigarettes day^{-1}, current >25 cigarettes day^{-1}, current occasional smoker of pipe, cigarettes or other types of tobacco, current/former smokers with unknown value of intensity or time since cessation and not specified). Other potential confounders were additionally adjusted for in multivariable model 2, such as BMI (kg m^{-2}), physical activity (inactive, moderately inactive, moderately active, active and not specified), highest educational level (none, primary school, technical/professional school, secondary school, university or higher and not specified) and alcohol intake (g day^{-1}). Any of these variables did not change effect estimates >10%, and therefore in the results we only show the multivariable model 1 because the results in both models were almost identical. The interactions between sex, BMI status (<25; 25–29.9; ⩾30 kg m^{-2}) or tobacco status (never, former and current smokers) and total and subclasses of flavonoid and lignan intakes were tested using likelihood ratio tests based on the models with and without the interaction terms. Sensitivity analyses were performed after exclusion of 181 cases who were diagnosed during the first 2 years of follow-up. *P*-values <0.05 (two-tailed) were considered significant. All analyses were conducted using SAS version 9.1 software (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Among 477 312 (29.8% men) participants included in this study, with a mean follow-up of 11.0 years, 1575 (70.3% men) incident primary bladder cancer cases were diagnosed, of which 1425 were

identified as UCC (including 430 aggressive, 413 non-aggressive and 52 unknown tumour aggressiveness UCC cases, and 530 unclassified cases; Table 1). The distribution of total and subclasses of flavonoid and lignan intakes and their main food sources is shown in the Table 2. The median intake of total flavonoids and total lignans were 332.4 mg day^{-1} and 1.3 mg day^{-1}, respectively. Descriptive characteristics of the population by quintiles of total flavonoid intake are shown in Table 3. There was a slightly greater percentage of men and higher age at recruitment in the fifth quintile compared with the first one. In addition, participants in the fifth quintile had the lowest BMI, reported higher total energy and alcohol. Furthermore, participants in the top quintile tended to smoke less, have a higher educational level and be more physically active compared with those in the bottom quintile.

Statistically significant inverse associations were found in the crude models between bladder cancer risk and the intake of total flavonoids, flavanols, flavan-3-ol monomers, proanthocyanidins, theaflavins, flavonols, flavones and lignans; although in multivariable models, only the intakes of flavonols (HR_{Q5-Q1} 0.75, 95% CI: 0.61–0.91; P-trend = 0.009) and lignans (HR_{Q5-Q1} 0.78, 95% CI: 0.62–0.96; P-trend = 0.042) maintained the significant inverse association with bladder cancer risk (Table 4).

Similar relationships were observed for UCC (Table 4), where only flavonol intake was inversely associated with UCC risk (HR_{Q5-Q1} 0.76, 95% CI: 0.62–0.94; P-trend = 0.022) and lignan intake tended to be inversely related to UCC risk (HR_{Q5-Q1} 0.79, 95% CI: 0.63–1.00; P-trend = 0.090) in the multivariable model. According to tumour stage and grade, flavonol (HR_{Q5-Q1} 0.64, 95% CI: 0.44–0.95; P-trend = 0.020) and lignan (HR_{Q5-Q1} 0.59, 95% CI: 0.39–0.89; P-trend = 0.035) intakes were inversely related to aggressive UCC, but not to non-aggressive UCC (Table 4).

There was no evidence that the relation between total flavonoid and lignan intake and bladder cancer was modified by sex (P for interaction = 0.19 and 0.23) or BMI (P for interaction = 0.52 and 0.30). Although the interactions with tobacco consumption were not significant for the intake of total flavonoids and lignans (P for interaction = 0.47 and 0.90, respectively), separate analyses were presented for smoking status because it is a major risk factor of bladder cancer (Supplementary Table 1). Similar results were observed between the intake of total and subclasses of flavonoids and lignans and bladder cancer risk (and subtypes) in never and current smokers.

In the sensitivity analysis, similar associations between the intake of flavonols (HR_{Q5-Q1} 0.69, 95% CI: 0.56–0.86; P-trend = 0.004) and lignans (HR_{Q5-Q1} 0.76, 95% CI: 0.60–0.97; P-trend = 0.055) and incidence of overall bladder cancer were observed after the exclusion of bladder cancer cases diagnosed within the first 2 years of follow-up.

DISCUSSION

The results in this large cohort of participants from 10 Western European countries suggest that higher dietary intakes of flavonols and lignans may be associated with an approximately 25% lower bladder cancer risk. These protective associations were also observed for UCC, in particular the aggressive tumours. No associations were observed with either total or other flavonoid subclasses.

To the best of our knowledge, there is only one other prospective epidemiological study on flavonoids and bladder cancer, which reported no association between flavan-3-ol monomers and bladder cancer risk in the Iowa Women's Health Study, a postmenopausal women cohort from the United States (Arts *et al*, 2002). Our finding provides further evidence for the absence of any strong association between flavan-3-ol monomers, one of the most abundant flavonoid subclasses, primarily found in tea, and bladder cancer risk in a cohort that contains more cancer cases (1575 *vs* 103) and includes men, who are at greater risk of developing bladder cancer (70.3% of bladder cases). Conversely to our results, in a Spanish case–control study, no association with some individual flavonols and flavones was observed, but the food composition table used in this study was quite old and therefore, very limited (Garcia *et al*, 1999). In relation to other cancers of the urinary tract, intake of flavonols and particularly quercetin was inversely associated with renal cell carcinoma risk in the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (Wilson *et al*, 2009) and in an Italian case–control study (Bosetti *et al*, 2007), but not total flavonoids. However, to our knowledge, there are no studies assessing the relationship between lignan intake and risk of urinary tract cancers.

A randomised controlled trial, with an intervention group that followed a month long diet rich in flavonoids from a typical Mediterranean diet and green tea, showed a strong correlation between urinary phenolics and an anti-mutagenicity activity, indicated by an inhibition effect of urinary extracts on *Salmonella typhimurium* mutations induced by MeIQx (as model substrate for cytochrome P4501A2) (Malaveille *et al*, 2004). From the same

Table 1. Distribution of participants and bladder cancer and UCC cases according to tumour aggressiveness during 11 years of follow-up in the 10 countries participating in the EPIC study

Country	All	Person-years	Bladder cancer cases	UCC cases	Aggressive UCC	Non-aggressive UCC
Denmark	55 016	601 466	303	284	112	80
France	67 385	699 360	31	24	13	6
Germany	48 583	480 614	199	171	46	40
Greece	26 032	247 711	45	25	5	6
Italy	44 541	500 407	183	143	45	42
Norway	35 169	342 279	24	24	8	2
Spain	40 002	482 582	146	138	24	61
Sweden	48 684	638 931	289	281	90	80
The Netherlands	36 505	431 252	104	101	30	29
United Kingdom	75 395	838 397	251	234	57	67
TOTAL	477 312	5 262 998	1575	1425	430	413

Abbreviations: EPIC = European Prospective Investigation into Cancer and Nutrition study; UCC = urothelial cell carcinoma.

Table 2. Dietary intake of flavonoids and lignans (in mg day^{-1}) and their main food sources in the EPIC study

	Mean	S.d.	Median	Percentile 5	Percentile 95	Food sources
Total flavonoids	437.2	335.0	332.4	90.8	1137.7	Fruits (40%), tea (19%), wine (12%), fruit juices (6%)
Flavanols	355.3	309.2	248.9	58.9	1013.4	Tea (44%), fruit (29%), wine (9%), chocolates (4%)
Flavan-3-ols monomers	176.6	253.5	46.4	9.4	731.5	Tea (84%), fruits (6%), wine (3%), chocolates (2%)
Proanthocyanidins	172.8	123.9	148.3	41.2	388.2	Fruits (53%), wine (14%), chocolates (6%), tea (4%)
Theaflavins	5.8	9.8	0.4	0	27.2	Tea (100%)
Anthocyanidins	28.3	22.5	22.5	5.4	70.4	Fruits (52%), wine (21%), vegetables (8%), fruit juices (7%)
Flavonols	27.2	17.3	22.4	8	61.8	Tea (26%), vegetables (23%), fruits (13%), soups (12%)
Flavanones	21.9	22.8	15.7	1.7	64.8	Fruits (50%), fruit juices (41%), wine (5%), vegetables (1%)
Flavones	3.5	4.1	2.5	0.4	9.8	Herbal tea (30%), wine (18%), fruits (16%), vegetables (15%)
Isoflavones	1.5	4.9	0.5	0.1	4.4	Soya products (40%), cakes (18%), cereals (11%), coffee (8%)
Lignans	1.5	0.8	1.3	0.6	2.9	Vegetables (24%), fruits (17%), cereals (16%), tea (10%)

Abbreviation: EPIC = European Prospective Investigation into Cancer and Nutrition study.

Table 3. Baseline characteristics of the participants in the EPIC study according to quintiles of total flavonoids intake

		Total flavonoid intake					
Characteristics	**All (*n* = 477 312)**	**Q1 (*n* = 95 462)**	**Q2 (*n* = 95 463)**	**Q3 (*n* = 95 462)**	**Q4 (*n* = 95 463)**	**Q5 (*n* = 95 462)**	***P*-value**
Median flavonoid intake (mg day^{-1})	332.4	123.9	225.4	332.4	514.6	933.4	
Sex, men (%)	29.8	29.7	29.8	29.1	29.5	30.9	<0.001
Age at enrolment (years)[a]	51.2 (9.9)	50.9 (9.1)	51.2 (9.6)	50.9 (9.6)	51.3 (9.9)	51.8 (11.3)	<0.001
BMI (kg m^{-2})[a]	25.4 (4.3)	25.7 (4.4)	25.8 (4.4)	25.6 (4.3)	25.3 (4.2)	24.8 (4.0)	<0.001
Energy intake (kcal day^{-1})[a]	2074 (619)	1791 (545)	2010 (569)	2142 (598)	2211 (638)	2217 (635)	<0.001
Alcohol intake (g day^{-1})[a]	11.9 (17.1)	7.5 (12.2)	10.6 (15.4)	12.4 (16.9)	14.5 (18.7)	14.7 (20.1)	<0.001
Educational level (%)							<0.001
No formal education	4.4	5.0	5.9	5.5	3.9	1.7	
Primary school	25.6	33.4	29.2	26.3	23.0	16.1	
Technical/professional school	22.3	27.2	22.1	19.0	20.0	23.1	
Secondary school	20.4	18.3	20.0	22.8	22.4	18.6	
University degree	23.8	15.0	21.1	24.3	26.9	31.6	
Not specified[b]	3.5	1.1	1.7	2.1	3.8	8.9	
Smoking status and intensity (%)							<0.001
Never smoker	43.0	36.4	43.0	44.3	44.6	46.8	
Current, <15 cigarretes day^{-1}	11.6	17.0	12.7	11.1	9.4	7.8	
Current, 15–25 cigarretes day^{-1}	6.3	11.2	6.9	5.5	4.4	3.2	
Current, 25 cigarretes day^{-1}	1.8	2.9	2.3	1.8	1.3	0.8	
Former, from ⩽10 years	9.6	9.9	9.5	9.4	9.7	9.3	
Former, from 11 to 20 years	8.2	6.8	7.7	8.1	9.0	9.2	
Former, from >20 years	7.9	6.6	7.0	6.8	8.2	10.9	
Current, pipe/cigar/occas	8.4	5.3	7.8	10.2	10.6	8.1	
Current/former, missing	1.6	1.7	1.5	1.3	1.5	2.1	
Not specified[b]	1.6	2.2	1.6	1.5	1.3	1.8	
Physical activity (%)							<0.001
Inactive	20.7	20.0	22.5	22.0	19.5	19.3	
Moderately inactive	31.3	24.8	31.2	33.7	34.2	32.8	
Moderately active	22.2	16.4	21.1	23.5	24.9	25.2	
Active	17.0	12.4	15.4	16.9	19.3	20.9	
Not specified[b]	8.8	26.4	9.8	3.9	2.1	1.8	

Abbreviations: BMI = body mass index; Current, pipe/cigar/occas = current occasional smoker of pipe, cigarettes or other types of tobacco; EPIC = European Prospective Investigation into Cancer and Nutrition study.
[a]Mean (s.d.).
[b]Not specified: details of educational level, smoking or physical activity not known.

Table 4. HRs and 95% CIs for bladder cancer, by quintiles of flavonoids in the EPIC study

		Bladder cancer			UCC			Aggressive UCC			Non-aggressive UCC		
		No of cases	Crude	Multivariable	No of cases	Crude	Multivariable	No of cases	Crude	Multivariable	No of cases	Crude	Multivariable
	Intake		HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)
Total flavonoids													
Quintile 1	<175.8	354	1 (ref)	1 (ref)	325	1 (ref)	1 (ref)	109	1 (ref)	1 (ref)	81	1 (ref)	1 (ref)
Quintile 2	175.8–275.8	326	0.91 (0.78–1.06)	1.01 (0.87–1.18)	293	0.92 (0.78–1.07)	1.02 (0.87–1.20)	91	0.87 (0.66–1.16)	0.98 (0.73–1.30)	77	1.00 (0.73–1.38)	1.16 (0.84–1.59)
Quintile 3	275.9–404.8	288	0.83 (0.70–0.98)	0.96 (0.81–1.14)	256	0.84 (0.71–0.99)	0.97 (0.82–1.16)	78	0.80 (0.59–1.09)	0.94 (0.69–1.28)	78	1.04 (0.75–1.44)	1.27 (0.91–1.77)
Quintile 4	404.9–658.4	289	0.75 (0.64–0.89)	0.91 (0.76–1.08)	259	0.77 (0.65–0.92)	0.93 (0.77–1.12)	72	0.71 (0.52–0.98)	0.86 (0.62–1.20)	86	1.00 (0.72–1.40)	1.30 (0.92–1.83)
Quintile 5	>658.4	318	0.75 (0.62–0.90)	0.91 (0.75–1.10)	292	0.75 (0.62–0.91)	0.92 (0.75–1.12)	80	0.69 (0.49–0.98)	0.86 (0.60–1.23)	91	0.95 (0.66–1.35)	1.26 (0.87–1.83)
P-trend			0.002	0.23		0.004	0.30		0.039	0.36		0.69	0.34
Continuous (log_2)			0.91 (0.86–0.95)	0.97 (0.92–1.03)		0.91 (0.86–0.96)	0.97 (0.92–1.03)		0.89 (0.81–0.99)	0.96 (0.87–1.07)		0.98 (0.88–1.09)	1.08 (0.97–1.20)
Flavanols													
Quintile 1	<122.3	345	1 (ref)	1 (ref)	318	1 (ref)	1 (ref)	104	1 (ref)	1 (ref)	76	1 (ref)	1 (ref)
Quintile 2	122.3–200.2	342	0.97 (0.84–1.13)	1.07 (0.92–1.25)	306	0.97 (0.83–1.13)	1.07 (0.91–1.25)	97	0.96 (0.73–1.27)	1.07 (0.80–1.42)	83	1.13 (0.83–1.55)	1.29 (0.94–1.77)
Quintile 3	200.3–311.1	267	0.74 (0.63–0.88)	0.86 (0.72–1.01)	238	0.74 (0.62–0.89)	0.86 (0.72–1.03)	70	0.71 (0.52–0.97)	0.83 (0.60–1.14)	77	1.02 (0.73–1.41)	1.23 (0.88–1.72)
Quintile 4	311.2–555.9	297	0.75 (0.63–0.89)	0.90 (0.77–1.07)	264	0.76 (0.63–0.90)	0.91 (0.76–1.09)	76	0.75 (0.54–1.03)	0.90 (0.65–1.26)	82	0.95 (0.67–1.33)	1.22 (0.86–1.73)
Quintile 5	>555.9	324	0.75 (0.62–0.90)	0.91 (0.75–1.10)	299	0.75 (0.62–0.90)	0.91 (0.75–1.12)	83	0.71 (0.50–1.00)	0.89 (0.62–1.27)	95	1.00 (0.70–1.44)	1.33 (0.92–1.94)
P-trend			0.002	0.25		<0.004	0.30		0.05	0.45		0.76	0.32
Continuous (log_2)			0.91 (0.87–0.95)	0.97 (0.92–1.02)		0.91 (0.87–0.95)	0.97 (0.92–1.02)		0.90 (0.83–0.98)	0.97 (0.88–1.06)		0.98 (0.90–1.08)	1.07 (0.97–1.18)
Flavan-3-ol monomers													
Quintile 1	<19.3	295	1 (ref)	1 (ref)	263	1 (ref)	1 (ref)	72	1 (ref)	1 (ref)	64	1 (ref)	1 (ref)
Quintile 2	19.3–33.8	318	0.84 (0.71–0.99)	0.91 (0.77–1.07)	284	0.83 (0.70–0.98)	0.91 (0.76–1.08)	90	0.94 (0.69–1.29)	1.04 (0.76–1.43)	75	0.92 (0.66–1.29)	1.04 (0.74–1.46)
Quintile 3	33.9–79.7	369	0.82 (0.70–0.96)	0.89 (0.76–1.06)	336	0.84 (0.71–1.00)	0.92 (0.77–1.10)	107	1.00 (0.73–1.37)	1.11 (0.81–1.54)	110	1.13 (0.82–1.56)	1.32 (0.95–1.84)
Quintile 4	79.8–376.0	263	0.72 (0.60–0.86)	0.83 (0.69–1.01)	234	0.71 (0.59–0.86)	0.83 (0.68–1.01)	71	0.79 (0.55–1.14)	0.95 (0.65–1.37)	76	0.99 (0.69–1.42)	1.24 (0.85–1.80)
Quintile 5	>376.0	330	0.74 (0.60–0.90)	0.90 (0.73–1.11)	308	0.74 (0.60–0.91)	0.90 (0.72–1.12)	90	0.80 (0.54–1.17)	1.02 (0.68–1.51)	88	0.93 (0.62–1.42)	1.23 (0.80–1.88)
P-trend			0.05	0.71		0.05	0.68		0.21	0.81		0.61	0.66
Continuous (log_2)			0.95 (0.92–0.98)	0.98 (0.95–1.01)		0.94 (0.91–0.98)	0.98 (0.95–1.01)		0.95 (0.89–1.01)	0.99 (0.93–1.05)		0.99 (0.93–1.06)	1.04 (0.97–1.11)
Proanthocyanidins													
Quintile 1	<82.8	370	1 (ref)	1 (ref)	341	1 (ref)	1 (ref)	114	1 (ref)	1 (ref)	78	1 (ref)	1 (ref)
Quintile 2	82.8–125.9	306	0.83 (0.71–0.97)	0.93 (0.79–1.08)	281	0.84 (0.72–0.99)	0.94 (0.80–1.11)	83	0.77 (0.58–1.03)	0.87 (0.65–1.16)	95	1.49 (1.1–2.02)	1.49 (1.10–2.02)
Quintile 3	126.0–171.9	303	0.84 (0.72–0.99)	0.97 (0.83–1.14)	277	0.86 (0.73–1.02)	1.00 (0.84–1.18)	99	0.96 (0.73–1.27)	1.12 (0.85–1.50)	75	1.32 (0.94–1.84)	1.32 (0.94–1.84)
Quintile 4	172.0–239.4	273	0.76 (0.65–0.90)	0.91 (0.76–1.08)	241	0.77 (0.64–0.91)	0.91 (0.76–1.09)	62	0.64 (0.46–0.88)	0.76 (0.54–1.07)	68	1.24 (0.87–1.77)	1.24 (0.87–1.77)
Quintile 5	>239.4	323	0.73 (0.62–0.87)	0.87 (0.73–1.05)	285	0.75 (0.63–0.90)	0.90 (0.74–1.09)	72	0.70 (0.50–0.98)	0.84 (0.59–1.20)	97	1.38 (0.96–1.99)	1.38 (0.96–1.99)
P-trend			<0.001	0.17		0.003	0.28		0.029	0.29		0.59	0.33
Continuous (log_2)			0.91 (0.86–0.96)	0.97 (0.92–1.03)		0.91 (0.86–0.96)	0.97 (0.92–1.03)		0.90 (80.82–0.99)	0.97 (0.87–1.07)		1.01 (0.91–1.12)	1.12 (1.00–1.25)

Table 4. (Continued)

		Bladder cancer			UCC			Aggressive UCC			Non-aggressive UCC		
		No of cases	Crude	Multivariable	No of cases	Crude	Multivariable	No of cases	Crude	Multivariable	No of cases	Crude	Multivariable
	Intake		HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)
Theaflavins													
Quintile 1	0	685	1 (ref)	1 (ref)	615	1 (ref)	1 (ref)	176	1 (ref)	1 (ref)	179	1 (ref)	1 (ref)
Quintile 2	0.1–0.6	225	0.82 (0.68–0.98)	0.86 (0.72–1.03)	203	0.86 (0.71–1.04)	0.91 (0.75–1.10)	67	0.92 (0.65–1.29)	0.97 (0.69–1.37)	53	0.96 (0.66–1.40)	1.01 (0.69–1.48)
Quintile 3	0.7–5.2	221	0.84 (0.70–1.00)	0.93 (0.78–1.11)	191	0.83 (0.69–1.01)	0.93 (0.77–1.13)	64	0.94 (0.67–1.31)	1.06 (0.75–1.49)	58	1.04 (0.73–1.49)	1.18 (0.82–1.69)
Quintile 4	5.3–14.7	217	0.75 (0.61–0.91)	0.88 (0.72–1.07)	203	0.77 (0.62–0.95)	0.91 (0.73–1.12)	57	0.79 (0.54–116)	0.94 (0.64–1.39)	67	1.06 (0.72–1.57)	1.28 (087–1.90)
Quintile 5	>14.7	227	0.72 (0.59–0.88)	0.86 (0.70–1.06)	213	0.74 (0.60–0.92)	0.89 (0.72–1.10)	66	0.77 (0.53–1.11)	0.94 (0.65–1.37)	56	0.80 (0.53–1.20)	0.97 (0.64–1.46)
P-trend			0.07	0.79		0.10	0.87		0.35	0.95		0.63	0.71
Continuous (log_2)			0.98 (0.97–0.99)	0.99 (0.98–1.01)		0.98 (0.97–1.00)	0.99 (0.98–1.01)		0.99 (0.97–1.01)	1.00 (0.98–1.02)		1.00 (0.97–1.02)	1.01 (0.99–1.04)
Anthocyanidins													
Quintile 1	<11.4	389	1 (ref)	1 (ref)	364	1 (ref)	1 (ref)	120	1 (ref)	1 (ref)	98	1 (ref)	1 (ref)
Quintile 2	11.4–18.6	365	1.04 (0.90–1.20)	1.15 (0.99–1.33)	333	1.03 (0.89–1.20)	1.14 (0.98–1.33)	105	1.05 (0.81–1.37)	1.17 (0.90–1.54)	90	1.09 (0.82–1.45)	1.24 (0.92–1.66)
Quintile 3	18.7–27.1	297	0.92 (0.78–1.07)	1.03 (0.88–1.21)	270	0.92 (0.78–1.08)	1.03 (0.88–1.22)	67	0.75 (0.56–1.02)	0.86 (0.63–1.17)	85	1.14 (0.84–1.53)	1.33 (0.98–1.80)
Quintile 4	27.2–41.6	289	0.99 (0.84–1.16)	1.12 (0.95–1.33)	246	0.94 (0.80–1.12)	1.08 (0.90–1.28)	76	1.03 (0.76–1.39)	1.17 (0.85–1.60)	66	1.00 (0.72–1.39)	1.21 (0.86–1.69)
Quintile 5	>41.6	235	0.94 (0.78–1.12)	1.05 (0.87–1.27)	212	0.97 (0.80–1.17)	1.09 (0.90–1.33)	62	1.06 (0.75–1.50)	1.20 (0.84–1.72)	74	1.21 (0.86–1.69)	1.46 (1.03–2.09)
P-trend			0.40	0.81		0.56	0.62		0.78	0.37		0.40	0.07
Continuous (log_2)			0.97 (0.92–1.01)	1.02 (0.97–1.07)		0.97 (0.93–1.02)	1.02 (0.97–1.07)		0.96 (0.88–1.05)	1.01 (0.93–1.11)		1.05 (0.96–1.15)	1.13 (1.03–1.24)
Flavonols													
Quintile 1	<12.9	353	1 (ref)	1 (ref)	319	1 (ref)	1 (ref)	101	1 (ref)	1 (ref)	77	1 (ref)	1 (ref)
Quintile 2	12.9–18.4	343	0.87 (0.74–1.01)	0.91 (0.78–1.06)	308	0.88 (0.75–1.03)	0.92 (0.79–1.09)	108	0.98 (0.74–1.30)	1.04 (0.78–1.37)	77	0.92 (0.67–1.28)	1.02 (0.74–1.41)
Quintile 3	18.5–25.9	300	0.75 (0.64–0.89)	0.81 (0.68–0.95)	268	0.78 (0.65–0.92)	0.84 (0.70–1.00)	71	0.65 (0.47–0.89)	0.69 (0.50–0.96)	91	1.08 (0.78–1.48)	1.25 (0.90–1.73)
Quintile 4	26.0–38.5	302	0.77 (0.65–0.91)	0.84 (0.70–1.00)	276	0.81 (0.67–0.96)	0.88 (0.73–1.07)	82	0.78 (0.55–1.06)	0.83 (0.59–1.16)	96	1.12 (0.80–1.57)	1.35 (0.95–1.91)
Quintile 5	>38.5	277	0.67 (0.56–0.81)	0.75 (0.61–0.91)	254	0.68 (0.56–0.84)	0.76 (0.62–0.94)	68	0.58 (0.41–0.84)	0.64 (0.44–0.95)	72	0.79 (0.54–1.16)	0.99 (0.66–1.48)
P-trend			<0.001	0.009		<0.001	0.022		0.003	0.020		0.26	0.88
Continuous (log_2)			0.88 (0.82–0.94)	0.92 (0.86–0.99)		0.89 (0.82–0.95)	0.93 (0.86–1.00)		0.86 (0.75–0.97)	0.90 (0.79–1.03)		0.95 (0.83–1.08)	1.04 (0.90–1.19)
Flavanones													
Quintile 1	<5.7	362	1 (ref)	1 (ref)	340	1 (ref)	1 (ref)	100	1 (ref)	1 (ref)	95	1 (ref)	1 (ref)
Quintile 2	5.7–11.9	316	1.03 (0.88–1.20)	1.11 (0.95–1.29)	281	0.99 (0.84–1.16)	1.07 (0.91–1.26)	84	0.96 (0.72–1.29)	1.06 (0.79–1.42)	78	1.05 (0.77–1.42)	1.15 (0.85–1.57)
Quintile 3	12.0–20.0	277	0.91 (0.78–1.07)	1.01 (0.86–1.18)	251	0.92 (0.77–1.08)	1.01 (0.85–1.19)	81	0.99 (0.74–1.34)	1.11 (0.82–1.50)	73	1.02 (0.74–1.39)	1.15 (0.84–1.58)
Quintile 4	20.1–33.0	322	1.02 (0.87–1.19)	1.14 (0.97–1.34)	292	1.03 (0.87–1.21)	1.15 (0.98–1.36)	87	1.06 (0.79–1.43)	1.21 (0.90–1.64)	92	1.16 (0.86–1.57)	1.34 (0.99–1.82)
Quintile 5	>33.0	298	0.91 (0.76–1.07)	1.04 (0.87–1.24)	261	0.89 (0.75–1.07)	1.03 (0.85–1.23)	78	0.98 (0.71–1.36)	1.14 (0.82–1.59)	75	0.89 (0.63–1.25)	1.08 (0.76–1.52)
P-trend			0.26	0.75		0.32	0.70		0.91	0.36		0.56	0.65
Continuous (log_2)			0.99 (0.96–1.02)	1.02 (0.99–1.05)		0.99 (0.96–1.02)	1.02 (0.99–1.06)		1.01 (0.95–1.07)	1.05 (0.98–1.11)		1.00 (0.95–1.06)	1.04 (0.98–1.11)

Table 4. (Continued)

		Bladder cancer			UCC			Aggressive UCC			Non-aggressive UCC		
		No of cases	Crude	Multivariable	No of cases	Crude	Multivariable	No of cases	Crude	Multivariable	No of cases	Crude	Multivariable
	Intake		HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)
Flavones													
Quintile 1	<1.1	388	1 (ref)	1 (ref)	355	1 (ref)	1 (ref)	115	1 (ref)	1 (ref)	99	1 (ref)	1 (ref)
Quintile 2	1.1–1.9	300	0.73 (0.62–0.85)	0.81 (0.69–0.95)	279	0.77 (0.65–0.91)	0.86 (0.73–1.02)	88	0.76 (0.57–1.02)	0.87 (0.65–1.16)	78	0.82 (0.59–1.12)	0.93 (0.67–1.28)
Quintile 3	2.0–3.0	310	0.76 (0.64–0.89)	0.87 (0.73–1.02)	285	0.80 (0.67–0.95)	0.92 (0.77–1.09)	84	0.76 (0.56–1.04)	0.89 (0.65–1.21)	86	0.92 (0.66–1.27)	1.08 (0.78–1.50)
Quintile 4	3.1–5.0	250	0.70 (0.59–0.83)	0.81 (0.68–0.97)	227	0.74 (0.62–0.89)	0.87 (0.77–1.04)	64	0.69 (0.50–0.96)	0.82 (0.58–1.15)	65	0.79 (0.56–1.12)	0.96 (0.68–1.36)
Quintile 5	>5.0	327	0.78 (0.66–0.93)	0.90 (0.76–1.08)	279	0.81 (0.67–0.97)	0.94 (0.78–1.13)	79	0.88 (0.64–1.23)	1.04 (0.74–1.45)	85	0.87 (0.62–1.22)	1.05 (0.74–1.50)
P-trend			0.10	0.73		0.14	0.85		0.73	0.63		0.63	0.68
Continuous (log_2)			0.95 (0.91–0.99)	0.99 (0.95—1.03)		0.95 (0.91–0.99)	0.99 (0.95–1.04)		0.96 (0.89–1.03)	1.01 (0.93–1.08)		0.99 (0.91–1.07)	1.04 (0.96–1.13)
Isoflavones													
Quintile 1	<0.2	203	1 (ref)	1 (ref)	174	1 (ref)	1 (ref)	58	1 (ref)	1 (ref)	47	1 (ref)	1 (ref)
Quintile 2	0.2–0.4	362	1.06 (0.88–1.28)	1.01 (0.83–1.22)	327	1.04 (0.85–1.27)	0.99 (0.81–1.21)	99	0.92 (0.65–1.30)	0.85 (0.60–1.21)	104	1.08 (0.75–1.55)	1.06 (0.74–1.53)
Quintile 3	0.5–0.6	388	1.09 (0.90–1.32)	1.01 (0.83–1.23)	345	1.03 (0.84–1.27)	0.96 (0.77–1.18)	107	0.97 (0.68–1.38)	0.85 (0.59–1.23)	109	1.03 (0.71–1.49)	1.01 (0.69–1.49)
Quintile 4	0.7–1.4	358	1.06 (0.86–1.31)	1.01 (0.81–1.26)	332	1.04 (0.83–1.29)	0.98 (0.78–1.24)	93	0.92 (0.62—1.36)	0.83 (0.55–1.26)	90	0.93 (0.62–1.40)	0.96 (0.62–1.47)
Quintile 5	>1.4	264	0.98 (0.77–1.25)	0.93 (0.72–1.21)	247	0.98 (0.76–1.26)	0.93 (0.71–1.22)	73	1.02 (0.65–1.59)	0.91 (0.56–1.48)	63	0.88 (0.55–1.41)	0.93 (0.56–1.55)
P-trend			0.42	0.41		0.57	0.57		0.67	0.76		0.39	0.64
Continuous (log_2)			0.98 (0.93–1.04)	0.97 (0.92–1.03)		0.98 (0.92–1.04)	0.97 (0.91–1.03)		1.02 (0.92–1.13)	1.00 (0.89–1.12)		0.90 (0.80–1.00)	0.90 (0.79–1.02)
Lignans													
Quintile 1	<0.9	323	1 (ref)	1 (ref)	296	1 (ref)	1 (ref)	96	1 (ref)	1 (ref)	81	1 (ref)	1 (ref)
Quintile 2	0.9–1.1	295	0.89 (0.75–1.04)	0.91 (0.77–1.07)	263	0.88 (0.74–1.05)	0.90 (0.76–1.07)	81	0.81 (0.59–1.09)	0.81 (0.60–1.10)	82	1.08 (0.78–1.47)	1.15 (0.83–1.58)
Quintile 3	1.2–1.4	283	0.81 (0.68–0.96)	0.83 (0.70–0.99)	250	0.81 (0.67–0.97)	0.83 (0.69–1.00)	68	0.63 (0.45–0.88)	0.63 (0.44–0.89)	70	0.91 (0.65–1.28)	1.00 (0.71–1.43)
Quintile 4	1.5–2.0	327	0.83 (0.69–1.00)	0.86 (0.71–1.04)	294	0.83 (0.68–1.01)	0.86 (0.70–1.05)	86	0.66 (0.46–0.93)	0.65 (0.45–0.94)	93	1.09 (0.76–1.55)	1.23 (0.85–1.79)
Quintile 5	>2.0	347	0.76 (0.62–0.92)	0.78 (0.62–0.96)	322	0.77 (0.63–0.95)	0.79 (0.63–1.00)	99	0.61 (0.42–0.89)	0.59 (0.39–0.89)	87	0.87 (0.59–1.29)	1.02 (0.67–1.57)
P-trend			0.015	0.042		0.037	0.09		0.032	0.035		0.40	0.93
Continuous (log_2)			0.89 (0.82–0.98)	0.91 (0.82–1.00)		0.90 (0.82–0.99)	0.92 (0.83–1.02)		0.87 (0.73–1.04)	0.87 (0.72–1.06)		0.90 (0.75–1.07)	0.97 (0.80–1.18)

Abbreviations: BMI = body mass index; CI = confidence interval; EPIC = European Prospective Investigation into Cancer and Nutrition study; HR = hazard ratio; UCC = urothelial cell carcinoma. Crude: stratified by sex, age (1 year) and centre. Multivariable: stratified by sex, age (1 year) and centre and adjusted for energy, smoking intensity, BMI, physical activity, alcohol intake and highest educational level.

study, an increase in flavonoid intake was associated with a decrease in DNA adducts, suggesting that a diet rich in flavonoids may reduce genotoxicity in the human urinary bladder (Talaska *et al*, 2006).

Epidemiological studies have suggested that a Mediterranean diet reduces the risk of cancers at different organ sites (World Research Cancer Fund and American Institute for Cancer Research, 2007); although, in a recent study in the EPIC cohort, no significant association was observed between adherence to the Mediterranean diet and risk of bladder cancer in the overall cohort (Buckland *et al*, 2014). However, in current smokers, a protective association was suggested. A high concentration of flavonoids and other polyphenols has been found in fruits and vegetables, red wine, and other elements of the Mediterranean diet (Perez-Jimenez *et al*, 2010). Despite this, there is inconsistent evidence on the role of total fruit and vegetable intakes measured by dietary questionnaires on bladder cancer risk (Sacerdote *et al*, 2007; Buchner *et al*, 2009; Ros *et al*, 2012; Park *et al*, 2013). However, intake of some vegetables subgroups was inversely associated with bladder cancer risk, such as root vegetables in previous EPIC studies (Buchner *et al*, 2009), particularly in aggressive UCC (Ros *et al*, 2012), and yellow-orange vegetables in the Multiethnic Cohort study (Park *et al*, 2013). It is worth bearing in mind that vegetables were the main food source of flavonols and lignans in this study. In addition, plasma concentrations of carotenoids (a nutritional biomarker of fruit and vegetable consumption and which are not limited by measurement errors inherent in dietary questionnaires) were inversely associated with bladder cancer risk (Ros *et al*, 2010). Therefore, several authors suggested that polyphenols and other antioxidant micronutrients may be, at least in part, responsible for the protective effect of the Mediterranean diet on health (Pelucchi *et al*, 2009; Giacosa *et al*, 2013).

A beverage that is not typical of the Mediterranean diet but has been related to bladder cancer protection and is rich in flavonoids is green tea (Wang *et al*, 2013). Green tea polyphenols have been shown to inhibit nitrosamine-mediated carcinogenesis in *in vitro* bladder models (Chung *et al*, 1993). Human studies have confirmed that green tea polyphenols interfere with carcinogenesis by reducing nitrosation and chromosome damage (Steele *et al*, 2000). Green tea is not widely consumed in Europe, and therefore was not in this study. Black tea is one of the main food sources of flavonols, but it is also the main source of other flavonoid subclasses (such as flavan-3-ol monomers and theaflavins) that were not related to bladder cancer in the present study. Therefore, our results suggest that flavonoids from black tea are not related to bladder carcinogenesis, as concluded by a previous meta-analysis (Wang *et al*, 2013).

In general, flavonoids and lignans can have a protective effect on bladder cancer through inhibition of phase I and induction of phase II enzymes. This protection may arise because of multiple mechanisms of action, further complexified by the synergistic behaviour of several compounds (Russo *et al*, 2012). In fact, in subjects with higher consumption of foods rich in flavonoids, a general upregulation of DNA repair genes has been observed, and an inverse correlation with gene expression levels, which may suggest a flavonoid-mediated reduction of DNA damage (Guarrera *et al*, 2007). However, other explanations are also plausible, three of which are: (i) flavonoids interfere with DNA repair; (ii) flavonoids can have a more complex interaction with DNA damage, not based on repair induction; and (iii) flavonoids can interfere with the induction/selection of chromosome instability or bulky DNA adducts by carcinogens.

In particular, individual flavonols have reduced proliferation of bladder cancer cells in *in vitro* models. Kaempferol (Xie *et al*, 2013) and myricetin (Sun *et al*, 2012) induced apoptosis in a dose-dependent manner by increasing the cleavage of caspase-3. Moreover, myricetin reduced the migration of human bladder cancer T24 cells and the phosphorylation of Akt and MMP-9 expression; whereas the phosphorylation of p38 MAPK was enhanced (Sun *et al*, 2012). In addition, quercetin reduced cancer progression by altering the extracellular catabolism of nucleotides in T24 cells (Rockenbach *et al*, 2013). No data are available on the effects of lignans upon bladder cancer cells.

In terms of our study limitations, first, changes in lifestyle could not be taken into account as we only collected baseline questionnaires of diet and other lifestyle variables. Second, measurement error in collecting self-reported dietary intake is inevitable, although centre-specific validated questionnaires (Riboli and Kaaks, 1997; Riboli *et al*, 2002) were used. Furthermore, flavonoid and lignan intakes are likely to be underestimated as the flavonoid database was incomplete (although an extensive common database was used) (Zamora-Ros *et al*, 2012, 2013) and herb/plant supplement intakes were omitted in these analyses (up to 5% in Denmark, the highest consumer country) (Skeie *et al*, 2009). This misclassification is likely to be random and therefore any association between intake and disease risk is likely underestimated. Nutritional biomarkers could be used to reduce this exposure misclassification (Zamora-Ros *et al*, 2014). Third, the association between dietary flavonoids and lignans with bladder cancer risk may be susceptible to confounding because high flavonoid and lignan intake reflects a healthier lifestyle. In our models, we have adjusted for other determinants of healthy lifestyle, however, possible residual confounding, especially due to smoking, cannot be excluded. Despite of that, similar risk estimates were observed in never and current smokers. Finally, we realise that our study is prone to the well-known drawback of multiple comparisons. The strengths of our multicentre study include its prospective and population-based design, detailed information on diet, large heterogeneity in flavonoid and lignan intake and a large sample of bladder cancer cases, with validated information on tumour aggressiveness.

In conclusion, this large prospective study conducted in 10 European countries suggests inverse associations between dietary intakes of flavonols and lignans and risk of bladder cancer, in particular aggressive tumours of UCC. No associations were observed with either total or other flavonoid subclasses.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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