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Associations of dietary carbohydrates, glycaemic index and glycaemic load with risk of bladder cancer: a case–control study

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Abstract

Carbohydrate foods with high glycaemic index (GI) and load (GL) may negatively influence cancer risk. We studied the association of dietary carbohydrates, GI, GL, intake of bread and pasta with risk of bladder cancer using data from an Italian case–control study. The study included 578 men and women with histologically confirmed bladder cancer and 608 controls admitted to the same hospitals as cases for acute, non-neoplastic conditions. OR were estimated by logistic regression models after allowance for relevant confounding factors. OR of bladder cancer for the highest *v.* the lowest quantile of intake were 1·52 (95 % CI 0·85, 2·69) for available carbohydrates, 1·18 (95 % CI 0·83, 1·67) for GI, 1·96 (95 % CI 1·16, 3·31, $P_{trend} < 0·01$) for GL, 1·58 (95 % CI 1·09, 2·29, $P_{trend} = 0·03$) for pasta and 1·92 (95 % CI 1·28, 2·86, $P_{trend} < 0·01$) for bread. OR for regular consumption of legumes and whole-grain products were 0·78 (95 % CI 0·60, 1·00) and 0·82 (95 % CI 0·63, 1·08), respectively. No heterogeneity in risks emerged across strata of sex. This case–control study showed that bladder cancer risk was directly associated with high dietary GL and with consumption of high quantity of refined carbohydrate foods, particularly bread. These associations were apparently stronger in subjects with low vegetable consumption.

Key words: Bladder cancer risk: Dietary glycaemic index: Pasta: Bread: Whole grains

Worldwide, bladder cancer is the most frequent malignant tumour of the urinary tract, with approximately 420 000 new cases each year with 4-fold higher incidence rates in men than in women[1]. Although tobacco smoking is the major risk factor for the development of bladder cancer accounting for up to 30–50 % of cases[2], hyperglycaemia and hyperinsulinaemia may play a role in initiation and progression.

Conditions characterised by long-term hyperinsulinaemia and hyperglycaemia, such as the metabolic syndrome and type 2 diabetes, have been identified as risk factors for bladder cancer incidence and mortality[3–7]. In particular, a 10-year prospective study including more than a million people found significantly higher mortality for bladder cancer in men with blood glucose levels >6·9 mmol/l, after adjusting for smoking, age and alcohol drinking[4]. Furthermore, poorly controlled glycaemia (glycated Hb (HbA1c) > 53 mmol/mol or > 7·0 %) in people with diabetes increased the risk of recurrence of specific types of bladder cancer compared with good glycaemic control (HbA1c < 53 mmol/mol or < 7·0 %)[8,9]. These data suggest that lifestyle factors promoting hyperglycaemia may play a role in

Abbreviations: GI, glycaemic index; GL, glycaemic load.

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bladder carcinogenesis. High glycaemic index (GI) and glycaemic load (GL) foods raise blood glucose levels even in the absence of diabetes, obesity and the metabolic syndrome. These foods increase blood glucose levels to a greater extent than the equivalent amount of carbohydrates consumed from low-GI foods[10]. High-GI diets have been associated with greater risk of cancer[11,12] including bladder cancer in North American populations[13,14].

To provide further information on the association between dietary GI/GL and bladder cancer risk in a Mediterranean area, we examined data from an Italian case–control study.

Methods

Study subjects

Between 2003 and 2014, we conducted a case–control study on bladder cancer within an established Italian network of collaborating centres, including Aviano and Milan in northern Italy, and Naples and Catania in southern Italy[15].

Cases were 690 patients aged between 25 and 84 years (median age: 67 years) with incident bladder cancer diagnosis, admitted to major general hospitals in the catchment areas. Nearly all cases (*n* 642, 93·0 %) were confirmed by histological testing on tumour tissue specimen from biopsy or surgery and three additional cases were confirmed by cytology only. Patients with self-reported history of diabetes mellitus (*n* 112) may include diet modification to control hyperglycaemia; therefore, they were excluded from the present analysis, leaving 578 cases (median age: 67 years).

Controls were 690 cancer-free patients aged between 27 and 84 years admitted to the same network of hospitals as cases for a wide spectrum of acute conditions unrelated to tobacco smoking, alcohol consumption or long-term diet modification. Controls were frequency-matched to cases by study centre, sex and age (in 5-year groups). In all, twenty-five controls were excluded after enrolment because of inappropriate admission diagnosis. After excluding subjects with self-reported history of diabetes mellitus (*n* 57), the total number of eligible controls was 608 (median age: 66 years). Of these, 28·3 % were admitted for traumatic disorders, 22·5 % for non-traumatic orthopaedic disorders, 38·7 % for acute surgical conditions and 10·5 % for other various illnesses. Less than 5 % of cases and controls approached for interview during their hospital stay refused to participate for personal reasons. The power was adequate to detect 80 % risk difference for variables with a prevalence of at least 20 %, at the usual 95 % confidence limit. The present study was conducted according to the guidelines laid down in the Declaration of Helsinki and reported according to the STROBE guidelines[16]. All procedures involving human subjects were approved by the Ethic Boards of each study centre (Centro di Riferimento Oncologico (CRO)-Aviano, University of Milan, National Cancer Institute Pascale). All study subjects signed an informed consent before interview.

Data collection

Trained interviewers administered a structured questionnaire to cases and controls during hospitalisation. It included information on age, education and other socio-demographic characteristics, anthropometric measures, selected lifestyle habits (e.g. tobacco smoking), personal medical history and family history of cancer. The presence of abdominal obesity was defined using the International Diabetes Federation cutoff points (waist circumference ≥94 cm for men and ≥80 cm for women). As the information on waist circumference could not be obtained for technical reasons in 135 cases and 173 controls, we considered the BMI ≥ 30 kg/m^2 as a proxy of abdominal obesity in patients missing waist circumference.

An interviewer-administered FFQ was used to assess dietary habits related to the 2 years preceding diagnosis/interview. This included seventy-eight foods, food groups or recipes (i.e. the most common ones in the Italian diet) structured into six sections: (i) bread, cereals and first courses; (ii) second courses (i.e. meat, fish and other main dishes); (iii) side dishes (i.e. vegetables); (iv) fruits; (v) desserts, sweets and soft drinks; (vi) milk, hot beverages and sweeteners. An additional section assessed the use of alcoholic beverages. Subjects were asked to indicate the average weekly frequency of consumption for each dietary item; intakes lower than once a week, but at least once a month, were coded as 0·5/week. For fruit and vegetables subject to seasonal variation, consumption in season and the corresponding duration were elicited. The serving size was defined in 'natural' unit (e.g. 1 egg) or as an average serving in the Italian diet (e.g. 50 g of salad, 150 g of tomatoes). The FFQ was successfully tested for validity[17] and reproducibility[18]. Total energy and carbohydrate intake was computed using an Italian food composition database[19].

Calculation of glycaemic index and glycaemic load

For each carbohydrate-containing food, we expressed GI as a percentage of the glycaemic response elicited using white bread as a standard food, using international GI tables[20]. The average daily GI of each subject was computed by summing the products of the GI value of one serving of each food times the average number of servings of that food consumed by the subject per week divided by the weekly available carbohydrate[20,21]. In order to take into account Italian cooking habits (e.g. pasta 'al dente'), Italian sources were used for a few local recipes[22]. Food items for which a GI had not been determined were assigned the GI of the closest comparable food (e.g. tangerines were assigned the same GI of oranges). A score for the daily average GL was computed by summing the products of the GI value of one serving of each food times the average number of servings of that food consumed by the subject per week.

Statistical analysis

OR for bladder cancer and the corresponding 95 % CI were estimated using unconditional logistic regression models including terms for matching variables (study centre, sex, quinquennia of age), and potential confounders including years of education (<7, 7–11, ≥12 years), smoking habits (never, former, current smokers of <20 and of ≥20 cigarettes/d), alcohol drinking (<14, 14–20, ≥20 drinks/week), abdominal obesity (yes/no) and total energy intake (kJ/d). GI, GL, available carbohydrates, bread and pasta were entered in the

models as quartiles based on the distribution of controls, using the lowest quartile as the reference category. Given the low consumption, legumes and whole-grain products were categorised as use *v.* abstinence. Tests for trend were based on the likelihood-ratio test between the models with and without a linear term for each variable of interest. Heterogeneity across strata was tested by comparing the models with and without an interaction term for such variable[23].

Results

Table 1 shows the distribution of cases and controls according to socio-demographic characteristics, smoking habits, alcohol drinking, abdominal obesity and total energy intake. Compared with never smokers, heavy smokers (i.e. ≥20 cigarettes/d) reported a 7-fold increase in bladder cancer risk (95 % CI 4·58, 11·04) with a significant risk trend for number of cigarettes ($P<0·01$). Patients with abdominal obesity showed a significantly higher risk of bladder cancer (OR 1·33; 95 % CI 1·05, 1·69) as compared with those without this condition. No significant association emerged for education, alcohol drinking and total energy intake.

Table 1. Distribution of 578 bladder cancer cases and 608 controls according to socio-demographic characteristics and selected variables (Numbers and percentages, odds ratios and 95 % confidence intervals)

	Cases		Controls			
	n	%	*n*	%	OR*	95 % CI
Sex†						
Man	491	85·0	513	84·4		
Woman	87	15·0	95	15·6		
Age (years)†						
<55	78	13·5	105	17·3		
55–59	53	9·2	68	11·2		
60–64	91	15·7	107	17·6		
65–69	137	23·7	129	21·2		
70–74	125	21·6	113	18·6		
≥75	94	16·3	86	14·1		
Study centre†						
Aviano	202	35·0	233	38·3		
Milan	200	34·6	212	34·9		
Naples	111	19·2	96	15·8		
Catania	65	11·2	67	11·0		
Education (years)‡						
<7	233	40·4	242	39·8	1§	
7–11	196	34·0	201	33·1	1·14	0·86, 1·52
≥12	148	25·6	165	27·1	1·05	0·77, 1·44
χ^2 for trend					$P_{\text{for trend}}=0·68$	
Smoking habits						
Never	85	14·7	218	35·8	1§	
Former	242	41·9	257	42·3	2·52	1·82, 3·49
Current (cigarettes/d)						
<20	139	24·0	81	13·3	5·26	3·57, 7·74
≥20	112	19·4	52	8·6	7·11	4·58, 11·04
χ^2 for trend					$P_{\text{for trend}}<0·01$	
Alcohol drinking (drinks/week)‡						
<14	243	42·1	272	44·8	1§	
14–20	185	32·1	197	32·5	1·05	0·80, 1·39
≥21	149	25·8	138	22·7	1·27	0·92, 1·76
χ^2 for trend					$P_{\text{for trend}}=0·16$	
Abdominal obesity						
No	246	42·6	296	48·7	1§	
Yes	332	57·4	312	51·3	1·33	1·05, 1·69
Total energy (kJ/d)					$P=0·02$	
<7840	141	24·4	152	25·0	1§	
7840 to <9360	138	23·9	152	25·0	1·02	0·73, 1·41
9360 to <11351	163	28·2	152	25·0	1·24	0·89, 1·73
≥11351	136	23·5	152	25·0	1·07	0·75, 1·53
χ^2 for trend					$P_{\text{for trend}}=0·46$	

* Estimated by logistic regression model adjusted for sex, age and study centre.
† Matching variable.
‡ The sum does not add up to total because of missing values, one case for education, one case and one control for alcohol.
§ Reference category.

Table 2 gives the OR for bladder cancer according to quartiles of available carbohydrates, GI, GL and selected carbohydrate-rich food groups. No significant associations emerged for total available carbohydrates (OR 1·52; 95 % CI 0·85, 2·69) and for GI (OR 1·18; 95 % CI 0·83, 1·67), whereas a significant direct association was observed for GL, with an OR of 1·96 (95 % CI 1·16, 3·31; $P_{\text{for trend}}<0·01$). Bread was directly associated with bladder cancer risk with OR of 1·64 (95 % CI 1·14, 2·35) and 1·92 (95 % CI 1·28, 2·86) for the third and fourth quartiles, respectively, compared with the lowest quartile ($P_{\text{for trend}}<0·01$). Similarly, elevated pasta consumption was associated with increased bladder cancer (OR 1·58; 95 % CI 1·09, 2·29 in the highest *v.* the lowest quartile of intake; $P_{\text{for trend}}=0·03$). The association with pasta was significant in men only (OR 1·81; 95 % CI 1·20, 2·73; $P_{\text{for trend}}<0·01$), but no heterogeneity was observed between men and women ($P=0·26$). Although not significant, high regular use of whole-grain products and legumes showed an inverse association with bladder cancer risk (OR 0·82; 95 % CI 0·63, 1·08 and OR 0·78; 95 % CI 0·60, 1·00, respectively), as compared with abstainers. No heterogeneity emerged according to sex ($P_{\text{for heterogeneity}}\geq 0·05$).

As vegetables and related seasoning, particularly olive oil, may counteract the glycaemic response of food, the associations between bladder cancer risk and available carbohydrates, GI, GL and intake of bread and pasta were further analysed in separate strata of vegetable intake (Table 3). Although no significant heterogeneity emerged for all the considered food items, results were suggestive that the effect for elevated GL was stronger among people with vegetable consumption below the median (i.e. 160 g/d) than among those above this level of consumption (OR 2·41 and 1·74, respectively).

Discussion

Our study found that high dietary GL, an indicator of both quality and quantity of carbohydrate foods, and high intakes of bread and pasta were directly associated with bladder cancer risk. Interestingly, these associations were less strong in people with elevated vegetable consumption.

Two other studies, one conducted in the USA and one in Canada, investigated the association of dietary GI and GL and bladder cancer risk and found an increased risk with higher GI but no association with GL[13,14]. The apparent discrepancy in results may be because of different dietary habits in different countries. In the US study, the first quantile of GL started at very low values compared with the present Italian population, where diets are very rich in total carbohydrates. The dietary GL is the product of each food's GI (derived from GI testing of foods in human subjects) by the amount of total available carbohydrates present in the same food (excluding unavailable carbohydrate

Table 2. Distribution of 578 bladder cancer cases (Ca) and 608 controls (Co), according to available carbohydrates, glycaemic index, glycaemic load, bread, pasta, legumes and whole-grain products
(Odds ratios and 95 % confidence intervals)

			Overall		Sex			
					Men		Women	
	Ca:Co	Median intake	OR*	95 % CI	OR*	95 % CI	OR*	95 % CI
Available carbohydrates (g/d)								
I (<223)	129:152	190	1†		1†		1†	
II (223 to <270)	161:152	248	1·62	1·12, 2·35	1·57	1·04, 2·36	1·90	0·73, 4·95
III (270 to <325)	157:152	294	1·65	1·09, 2·51	1·50	0·95, 2·34	2·32	0·69, 7·83
IV (≥325)	131:152	379	1·52	0·85, 2·69	1·42	0·77, 2·63	2·07	0·32, 13·38
χ^2 for trend			$P = 0·10$		$P = 0·26$		$P = 0·25$	
					χ^2 for heterogeneity: $P = 0·86$			
Glycaemic index								
I (<75)	136:152	72	1†		1†		1†	
II (75 to <79)	135:152	77	1·07	0·75, 1·52	1·10	0·74, 1·62	1·06	0·45, 2·50
III (79 to <83)	140:152	81	1·03	0·73, 1·46	1·07	0·73, 1·57	0·84	0·34, 2·08
IV (≥83)	167:152	86	1·18	0·83, 1·67	1·18	0·80, 1·73	1·46	0·53, 4·02
χ^2 for trend			$P = 0·44$		$P = 0·46$		$P = 0·70$	
					χ^2 for heterogeneity: $P = 0·94$			
Glycaemic load								
I (<169)	123:152	145	1†		1†		1†	
II (169 to <210)	145:152	191	1·61	1·11, 2·34	1·54	1·02, 2·33	2·12	0·82, 5·48
III (210 to <257)	166:152	229	2·03	1·36, 3·04	1·94	1·25, 3·00	2·66	0·86, 8·21
IV (≥257)	144:152	302	1·96	1·16, 3·31	1·85	1·05, 3·26	2·82	0·56, 14·19
χ^2 for trend			$P < 0·01$		$P = 0·01$		$P = 0·14$	
					χ^2 for heterogeneity: $P = 0·83$			
Bread (g/d)‡								
I (<54)	112:153	43	1†		1†		1†	
II (54 to <102)	132:143	89	1·44	0·99, 2·08	1·51	1·00, 2·29	1·26	0·53, 2·95
III (102 to <154)	168:167	118	1·64	1·14, 2·35	1·65	1·11, 2·48	1·68	0·70, 4·03
IV (≥154)	166:145	206	1·92	1·28, 2·86	1·79	1·16, 2·77	4·31	1·08, 17·21
χ^2 for trend			$P < 0·01$		$P = 0·01$		$P = 0·05$	
					χ^2 for heterogeneity: $P = 0·67$			
Pasta (g/d)§‖								
I (<43)	158:167	34	1†		1†		1†	
II (43 to <57)	116:134	49	1·19	0·82, 1·73	1·32	0·88, 2·00	0·77	0·30, 2·01
III (57 to <70)	135:160	63	1·12	0·78, 1·61	1·29	0·86, 1·93	0·62	0·25, 1·58
IV (≥70)	169:147	83	1·58	1·09, 2·29	1·81	1·20, 2·73	1·08	0·40, 2·90
χ^2 for trend			$P = 0·03$		$P < 0·01$		$P = 0·91$	
					χ^2 for heterogeneity: $P = 0·26$			
Legumes (g/d)‖								
Abstainers	374:353	0	1†		1†		1†	
Regular users	204:255	14	0·78	0·60, 1·00	0·79	0·60, 1·05	0·67	0·33, 1·37
					χ^2 for heterogeneity: $P = 0·68$			
Whole-grain products (g/d)								
Abstainers	410:393	0	1†		1†		1†	
Regular users	168:215	43	0·82	0·63, 1·08	0·76	0·56, 1·03	1·24	0·63, 2·45
					χ^2 for heterogeneity: $P = 0·20$			

* Estimated by logistic regression model, adjusted for sex, age, study centre, education, smoking habits, alcohol drinking, abdominal obesity and total energy.
† Reference category.
‡ Includes also crackers and bread sticks.
§ Includes also rice.
‖ Uncooked.

such as fibre). A low-GL diet can be achieved by either consuming low-GI foods or by consuming small amounts of carbohydrate foods with any GI value or by consuming both low-GI foods and small quantity of carbohydrate foods. Considering that the Mediterranean–Italian diet is characterised by frequent (e.g. daily) consumption of pasta (a medium–low GI food), a high GL in Italy may be the result of very large quantities of carbohydrates. High-carbohydrate diets, as typically seen in Italy, may need to include very low-GI foods to show an impact on glycaemia. With the shift of the Mediterranean diet towards more convenient and fast food choices, lower-GI foods such as legumes, have become less frequent on the plates of many Italians[24]. It is possible that in bladder cancer a high carbohydrate intake may confound any potential association with GI. Diets with low GI (<69 on a bread scale) and low GL are considered more beneficial to overall health, especially in environments characterised by sedentary behaviour, excess energy intake and excess body weight[25]. Reducing the glycaemic impact of the overall diet with low-GI/GL foods has been shown to decrease concentrations of fasting

Table 3. Distribution of 578 bladder cancer cases and 608 controls, according to quartiles of available carbohydrates, glycaemic index, glycaemic load, consumption of bread and pasta, in strata of vegetable intake
(Odds ratios and 95 % confidence intervals)

		Vegetable intake (g/d)			
		<160		≥160	
	Median intake	OR*	95 % CI	OR*	95 % CI
Available carbohydrates (g/d)					
I (<223)	190	1†		1†	
II (223 to <270)	248	1·35	0·83, 2·18	2·14	1·10, 4·17
III (270 to <325)	294	1·86	1·02, 3·40	1·64	0·84, 3·20
IV (≥325)	379	1·67	0·68, 4·06	1·50	0·64, 3·52
χ^2 for trend		$P = 0·09$		$P = 0·61$	
		χ^2 for heterogeneity: $P = 0·70$			
Glycaemic index					
I (<75)	72	1†		1†	
II (75 to <79)	77	1·36	0·83, 2·24	0·91	0·54, 1·53
III (79 to <83)	81	1·41	0·86, 2·32	0·80	0·47, 1·34
IV (≥83)	86	1·35	0·82, 2·22	0·93	0·54, 1·60
χ^2 for trend		$P = 0·26$		$P = 0·65$	
		χ^2 for heterogeneity: $P = 0·18$			
Glycaemic load					
I (<169)	145	1†		1†	
II (169 to <210)	191	1·43	0·88, 2·32	2·01	1·04, 3·88
III (210 to <257)	229	2·24	1·26, 3·99	1·93	1·01, 3·69
IV (≥257)	302	2·41	1·06, 5·47	1·74	0·80, 3·77
χ^2 for trend		$P < 0·01$		$P = 0·25$	
		χ^2 for heterogeneity: $P = 0·77$			
Bread (g/d)‡					
I (<54)	43	1†		1†	
II (54 to <102)	89	1·37	0·85, 2·21	1·49	0·81, 2·75
III (102 to <154)	118	1·71	1·05, 2·77	1·44	0·80, 2·58
IV (≥154)	206	1·83	1·02, 3·31	1·85	1·01, 3·39
χ^2 for trend		$P = 0·02$		$P = 0·07$	
		χ^2 for heterogeneity: $P = 0·96$			
Pasta (g/d)§‖					
I (<43)	34	1†		1†	
II (43 to <57)	49	1·06	0·65, 1·72	1·40	0·75, 2·60
III (57 to <70)	63	1·04	0·65, 1·67	1·19	0·65, 2·19
IV (≥70)	83	1·73	1·03, 2·92	1·55	0·86, 2·79
χ^2 for trend		$P = 0·07$		$P = 0·20$	
		χ^2 for heterogeneity: $P = 0·86$			

* Estimated by logistic regression model, adjusted for sex, age, study centre, education, smoking habits, alcohol drinking, abdominal obesity and total energy.
† Reference category.
‡ Includes also crackers and bread sticks.
§ Includes also rice
‖ Uncooked.

blood glucose, glycosylated proteins, insulin and inflammatory markers, and to reduce the risk of developing type 2 diabetes and some cancers[14,25]. Fasting hyperglycaemia (>7·0 mmol/l) has been found to significantly increase bladder cancer risk in an Asian study including 1·3 million people aged 30–95 years[4]. Insulin can activate epidermal growth factors and protein kinases and in *in vitro* studies insulin increased bladder cancer cell proliferation in a time- and dose-dependent manner[26,27]. The diabetic medication metformin, which helps to control both glycaemia and insulin resistance, has been shown to reduce growth of malignant cell types including bladder cancer cells[28,29]. It is also possible that diets promoting large increases in blood glucose may promote urinary tract infections and hence increase bladder cancer risk[30].

Two main staple carbohydrate foods of the Italian Mediterranean diet are bread (high GI) and pasta (medium–low GI), representing 24 and 16 % of total carbohydrate intake, respectively[31]. Generally, the associations with cancer risk have been stronger for bread than for pasta[32,33] and with a difference between sexes. In a previous Italian study investigating the association of pasta or bread and colorectal or breast cancer, the associations with bread were stronger in women than in men[32]. In the current study, bread, pasta and GL were directly and significantly associated with bladder cancer particularly in men. Men are generally affected by bladder cancer three to four times more often than women[34,35], and several *in vitro* and animal studies suggest a potential involvement of sex steroid hormonal pathways[36]. Indeed, recent evidence suggests that androgen and androgen receptor may contribute to bladder carcinogenesis both through hormonal pathways and by other mechanisms such as reduced expression of detoxifying enzymes in the bladder[37,38]. It is possible that diets that increase blood glucose the most may favour higher testosterone bioavailability by reducing its binding protein[39].

Furthermore, the results of our study suggest that the associations between bladder cancer risk and GL may be stronger among people with a lower vegetable intake (<160 g/d) than in those with higher intakes (>160 g/d), possibly because of components present in vegetables (e.g. fibre and antioxidants) or consumed with vegetables (e.g. olive oil) that may modify the glycaemic response by various mechanisms (e.g. slowing carbohydrate absorption or reducing glucose toxicity to the beta cells)[40,41].

As for most case–control studies, information and selection biases were potential limitations of this study. Information bias, however, was minimised by the administration of the questionnaire to both cases and controls by the same trained interviewers, under similar conditions in a hospital setting. Differential recall in cases and controls in our study may be unlikely as the dietary hypothesis of GI and GL in bladder cancer risk was not known during the study and the questionnaire was satisfactorily reproducible[42]. However, as the information was collected after diagnosis, it is possible that early symptoms of the disease may have caused changes in the diet. To avoid these potential sources of bias, any relevant dietary change in the 2 years preceding interview were recorded and we excluded from the control group all subjects with diagnoses that might have implicated long-term dietary modifications (e.g. diabetes). Furthermore, a possible limiting factor in our analyses was for the calculation of abdominal obesity where waist circumference was missing in approximately 25 % of cases and controls and BMI ≥ 30 kg/m^2 was used as a proxy. BMI ≥ 30 kg/m^2 is considered a good proxy of abdominal obesity, and analyses conducted excluding patients with missing waist circumference did not show appreciable variation in risk magnitude. In addition, GI and GL values may have some variability according to specific foods and cooking methods. In particular, although pasta and rice have different glycaemic responses, they were assessed together in our FFQ. However, this information bias is unlikely to have an impact on risk estimates, as rice accounts for <20 % in this food group of this study population[43]. The almost complete participation of identified cases and controls, and the use of a validated and reproducible questionnaire, contributed to strengthen our findings. Generalisability of our study results has the limitations discussed above, typical of a hospital case–control study.

In conclusion, this study showed that bladder cancer risk is directly associated with high dietary GL and with consumption of high quantity of refined carbohydrates. These associations were stronger in subjects reporting low vegetable consumption.

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References

1. Forman D, Bray F, Brewster DH, *et al.* (2013) *Cancer Incidence in Five Continents*, Vol. X. Lyon: IARC Scientific Publication.
2. Freedman ND, Silverman DT, Hollenbeck AR, *et al.* (2011) Association between smoking and risk of bladder cancer among men and women. *JAMA* **306**, 737–745.
3. Esposito K, Chiodini P, Colao A, *et al.* (2012) Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. *Diabetes Care* **35**, 2402–2411.
4. Jee SH, Ohrr H, Sull JW, *et al.* (2005) Fasting serum glucose level and cancer risk in Korean men and women. *JAMA* **293**, 194–202.
5. Montella M, Di Maso M, Crispo A, *et al.* (2015) Metabolic syndrome and the risk of urothelial carcinoma of the bladder: a case-control study. *BMC Cancer* **15**, 720.
6. Turati F, Polesel J, Di Maso M, *et al.* (2015) Diabetes mellitus and the risk of bladder cancer: an Italian case-control study. *Br J Cancer* **113**, 127–130.
7. Zhu Z, Zhang X, Shen Z, *et al.* (2013) Diabetes mellitus and risk of bladder cancer: a meta-analysis of cohort studies. *PLOS ONE* **8**, e56662.
8. Hwang EC, Kim YJ, Hwang IS, *et al.* (2011) Impact of diabetes mellitus on recurrence and progression in patients with non-muscle invasive bladder carcinoma: a retrospective cohort study. *Int J Urol* **18**, 769–776.
9. Tai YS, Chen CH, Huang CY, *et al.* (2015) Diabetes mellitus with poor glycemic control increases bladder cancer recurrence risk in patients with upper urinary tract urothelial carcinoma. *Diabetes Metab Res Rev* **31**, 307–314.
10. Jenkins DJ, Wolever TM, Taylor RH, *et al.* (1981) Glycemic index of foods: a physiological basis for carbohydrate exchange. *Am J Clin Nutr* **34**, 362–366.
11. Barclay AW, Petocz P, McMillan-Price J, *et al.* (2008) Glycemic index, glycemic load, and chronic disease risk–a meta-analysis of observational studies. *Am J Clin Nutr* **87**, 627–637.
12. Choi Y, Giovannucci E & Lee JE (2012) Glycaemic index and glycaemic load in relation to risk of diabetes-related cancers: a meta-analysis. *Br J Nutr* **108**, 1934–1947.
13. George SM, Mayne ST, Leitzmann MF, *et al.* (2009) Dietary glycemic index, glycemic load, and risk of cancer: a prospective cohort study. *Am J Epidemiol* **169**, 462–472.
14. Hu J, La Vecchia C, Augustin LS, *et al.* (2013) Glycemic index, glycemic load and cancer risk. *Ann Oncol* **24**, 245–251.
15. Polesel J, Bosetti C, Di Maso M, *et al.* (2014) Duration and intensity of tobacco smoking and the risk of papillary and non-papillary transitional cell carcinoma of the bladder. *Cancer Causes Control* **25**, 1151–1158.
16. von Elm E, Altman DG, Egger M, *et al.* (2007) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* **147**, 573–577.
17. Decarli A, Franceschi S, Ferraroni M, *et al.* (1996) Validation of a food-frequency questionnaire to assess dietary intakes in cancer studies in Italy. Results for specific nutrients. *Ann Epidemiol* **6**, 110–118.
18. Franceschi S, Negri E, Salvini S, *et al.* (1993) Reproducibility of an Italian food frequency questionnaire for cancer studies: results for specific food items. *Eur J Cancer* **29A**, 2298–2305.
19. Gnagnarella P, Parpinel M, Salvini S, *et al.* (2004) The update of the Italian food composition database. *J Food Comp Anal* **17**, 509–522.
20. Atkinson FS, Foster-Powell K & Brand-Miller JC (2008) International tables of glycemic index and glycemic load values: 2008. *Diabetes Care* **31**, 2281–2283.
21. Wolever TM, Nguyen PM, Chiasson JL, *et al.* (1994) Determinants of diet glycemic index calculated retrospectively from diet records of 342 individuals with non-insulin-dependent diabetes mellitus. *Am J Clin Nutr* **59**, 1265–1269.
22. Brighenti F & Casiraghi M (1992) Influenza dei processi di trasformazione sulla risposta glicemica ad alimenti amidacei. *G Ital Nutrizione Clin Prev* **1**, 79–87.
23. Breslow NE & Day NE (1980) Statistical methods in cancer research. Volume I –the analysis of case-control studies. *IARC Sci Publ* **32**, 5–338.
24. Giampaoli S, Krogh V, Grioni S, *et al.* (2015) Eating behaviours of Italian adults: results of the Osservatorio epidemiologico cardiovascolare/Health Examination Survey. *Epidemiol Prev* **39**, 373–379.
25. Augustin LS, Kendall CW, Jenkins DJ, *et al.* (2015) Glycemic index, glycemic load and glycemic response: An International Scientific Consensus Summit from the International Carbohydrate Quality Consortium (ICQC). *Nutr Metab Cardiovasc Dis* **25**, 795–815.
26. Liu S, Li Y, Lin T, *et al.* (2011) High dose human insulin and insulin glargine promote T24 bladder cancer cell proliferation via PI3K-independent activation of Akt. *Diab Res Clin Pract* **91**, 177–182.
27. Ornskov D, Nexo E & Sorensen BS (2006) Insulin-induced proliferation of bladder cancer cells is mediated through activation of the epidermal growth factor system. *FEBS J* **273**, 5479–5489.
28. Zhang T, Guo P, Zhang Y, *et al.* (2013) The antidiabetic drug metformin inhibits the proliferation of bladder cancer cells *in vitro* and *in vivo*. *Int J Mol Sci* **14**, 24603–24618.
29. Soranna D, Scotti L, Zambon A, *et al.* (2012) Cancer risk associated with use of metformin and sulfonylurea in type 2 diabetes: a meta-analysis. *Oncologist* **17**, 813–822.
30. Brown JS, Wessells H, Chancellor MB, *et al.* (2005) Urologic complications of diabetes. *Diabetes Care* **28**, 177–185.
31. Sette S, Le Donne C, Piccinelli R, *et al.* (2013) The third National Food Consumption Survey, INRAN-SCAI 2005-06: major dietary sources of nutrients in Italy. *Int J Food Sci Nutr* **64**, 1014–1021.
32. Augustin LS, Malerba S, Lugo A, *et al.* (2013) Associations of bread and pasta with the risk of cancer of the breast and colorectum. *Ann Oncol* **24**, 3094–3099.
33. Farvid MS, Cho E, Eliassen AH, *et al.* (2016) Lifetime grain consumption and breast cancer risk. *Breast Cancer Res Treat* **159**, 335–345.
34. Hartge P, Harvey EB, Linehan WM, *et al.* (1990) Unexplained excess risk of bladder cancer in men. *J Natl Cancer Inst* **82**, 1636–1640.
35. Torre LA, Siegel RL, Ward EM, *et al.* (2016) Global cancer incidence and mortality rates and trends–an update. *Cancer Epidemiol Biomarkers Prev* **25**, 16–27.
36. Godoy G, Gakis G, Smith CL, *et al.* (2016) Effects of androgen and estrogen receptor signaling pathways on

bladder cancer initiation and progression. *Bladder Cancer* **2**, 127–137.
37. Izumi K, Zheng Y, Hsu JW, *et al.* (2013) Androgen receptor signals regulate UDP-glucuronosyltransferases in the urinary bladder: a potential mechanism of androgen-induced bladder carcinogenesis. *Mol Carcinog* **52**, 94–102.
38. Miyamoto H, Yang Z, Chen YT, *et al.* (2007) Promotion of bladder cancer development and progression by androgen receptor signals. *J Natl Cancer Inst* **99**, 558–568.
39. Boering M, van Dijk PR, Logtenberg SJ, *et al.* (2016) Effects of intraperitoneal insulin versus subcutaneous insulin administration on sex hormone-binding globulin concentrations in patients with type 1 diabetes mellitus. *Endocr Connect* **5**, 136–142.
40. Augustin LS, Franceschi S, Jenkins DJ, *et al.* (2002) Glycemic index in chronic disease: a review. *Eur J Clin Nutr* **56**, 1049–1071.
41. Satija A, Bhupathiraju SN, Rimm EB, *et al.* (2016) Plant-based dietary patterns and incidence of type 2 diabetes in US men and women: results from three prospective cohort studies. *PLoS Med* **13**, e1002039.
42. D'Avanzo B, La Vecchia C, Katsouyanni K, *et al.* (1997) An assessment, and reproducibility of food frequency data provided by hospital controls. *Eur J Cancer Prev* **6**, 288–293.
43. Turrini A, Saba A, Perrone D, *et al.* (2001) Food consumption patterns in Italy: the INN-CA Study 1994–1996. *Eur J Clin Nutr* **55**, 571–588.

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