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Food consumption, meat cooking methods and diet diversity and the risk of bladder cancer

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ABSTRACT

Background: Since food metabolites are eliminated by the urinary tract, several studies have investigated the association between diet and bladder cancer risk. Recently, the World Cancer Research Fund International/American Institute for Cancer Research (WCRF/AICR) suggested a potential beneficial effect of some foods (mainly vegetables, fruit, and milk) in the development of bladder cancer. We investigated the association between food groups and bladder cancer risk, seeking insights into food diversity as well as meat cooking methods.

Methods: Data were derived from an Italian multicentre case–control study, conducted between 2003 and 2014, including 690 bladder cancer cases and 665 frequency-matched controls. Odds ratios (ORs) and the corresponding 95% confidence intervals (95%CIs) for various dietary aspects were estimated by unconditional logistic regression models adjusted for energy intake and the major known risk factors for bladder cancer.

Results: Comparing the highest versus the lowest quartiles, consumption of vegetables (OR = 0.62; 95%CI: 0.44-0.88) and milk/yogurt (OR = 0.62; 95%CI: 0.44–0.87) reduced the risk of bladder cancer. Conversely, consumption of meat increased bladder cancer risk with an OR of 1.57 (95%CI: 1.07–2.31), particularly when the meat was stewed (OR = 1.47; 95%CI: 1.03–2.09) or roasted (OR = 1.41; 95%CI: 1.00–1.99). There was a suggestion that a diversified diet reduced the risk of bladder cancer, but this was not significant.

Conclusions: Our study consolidates the role of diet in bladder cancer aetiology, showing a reduced risk for vegetable and milk/yogurt consumption and an increased risk for meat consumption, especially when the meat is stewed or roasted.

1. Introduction

Recognised risk factors for bladder cancer include tobacco smoking, occupational or environmental exposure to aromatic amines, polycyclic aromatic hydrocarbons or arsenic, and infection with *Schistomosa haematobium* [1–5]. Other potential risk factors are chronic bladder infections, phenacetin-containing analgesics, metabolic syndrome, diabetes mellitus, and genetic factors [6–9].

Since food metabolites are excreted through the urinary tract [10], a mounting number of studies have investigated the role of diet in the development of bladder cancer [11]. In 2015, the World Cancer Research Fund International/American Institute for Cancer Research (WCRF/AICR) concluded that the evidence of an inverse relationship between intake of vegetables and fruit and the incidence of bladder cancer was 'limited but suggestive'. Furthermore, the WCRF/AICR suggested a possible beneficial role of milk, although the evidence is not

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conclusive [11]. Other possible associations between diet and bladder cancer risk involve meat [12,13] and several micronutrients such as vitamins A, C and E, folate, carotenoids, and flavonoids [1,14,15].

Differences in the levels of food consumption and in cooking methods due to geographic variation may substantially modify the association between food consumption and cancer risk because of different baseline risks. For instance, the diet of populations from the Mediterranean area is characterised by an elevated consumption of fruits, vegetables, legumes, wholegrains, and vegetable fats (mainly olive oil), and it has generally been associated with a decreased risk of cancer [16], including bladder cancer [17].

The present Italian case–control study investigated the association between a wide range of food groups and bladder cancer risk, seeking insights into food diversity. Furthermore, meat consumption was investigated with a specific focus on cooking methods.

2. Material and methods

2.1. Study design and subject collection

Between 2003 and 2014 we conducted a multicentre case–control study on urothelial carcinoma of the bladder within an established Italian network of collaborating centres, including the province of Pordenone and the greater Milan area in northern Italy, and the urban areas of Naples and Catania in southern Italy. Study design, inclusion criteria, and histological examinations of the bladder tissue for diagnostic purposes have been described elsewhere [18]. Briefly, cases included 690 patients aged 25–84 years (median age: 67 years) with incident and histologically confirmed diagnosis of urothelial carcinoma of the bladder, recruited in the major general hospitals of the catchment areas. Controls were 665 cancer-free subjects aged 27–84 years (median age: 66 years) frequency matched to cases according to study centre, sex, and 5-year age groups. The control group was identified in the same network of hospitals as the cases and was selected among patients admitted for a wide spectrum of acute conditions unrelated to known or suspected risk factors for bladder cancer or to long-term diet modifications. Overall, 28.9% of the controls were admitted for traumas, 22.1% for non-traumatic orthopaedic disorders, 39.9% for acute surgical conditions, and 9.8% for miscellaneous other illnesses. All study participants signed an informed consent, according to the recommendations of the Board of Ethics of the study hospitals. More than 95% of eligible cases and controls agreed to participate in the study.

2.2. Diet assessment

Trained interviewers administered a structured questionnaire to study participants during their hospital stay. The questionnaire collected information on sociodemographic characteristics, anthropometric measures, lifestyle factors (i.e. tobacco smoking, alcohol drinking), occupational exposure to chemicals, medical history, drug use, and dietary habits. A validated [19,20] and reproducible [20–22] food frequency questionnaire (FFQ) was used to assess subjects' habitual diet 2 years prior to diagnosis (cases) or hospital admission (controls). The FFQ included information on weekly intake of various foods and recipes according to the following sections: (a) milk and sweeteners; (b) bread, cereals and first courses (including soups); (c) second courses (e.g., meat, fish, and other main dishes); (d) side dishes (vegetables and potatoes); (e) fruit; and (f) sweets and desserts. Four additional sections investigated lifetime consumption of beverages, namely (a) alcoholic beverages (wine, beer, aperitifs, and hard liquor); (b) hot beverages (coffee, cappuccino, tea, and herbal tea); (c) soft drinks (cola, energy and other carbonated drinks); and (e) tap and bottled water [23]. Serving size was defined either in 'natural' units (e.g., one apple, one cup of milk, one teaspoon of sugar, one egg) or as an average serving in the Italian diet (e.g., 80 g of pasta; 100 g of salad; 125 g of boiled potatoes; 120 g of beef steak). Occasional consumption (i.e., foods or recipes consumed less than once a week but at least once a month) was coded as 0.5 per week. Seasonal variation in fruit and vegetable consumptions was also considered to account for the fluctuations within the year. Total energy intake was computed using an Italian food composition database [24].

Table 1
Distribution of 690 cases of bladder cancer and 665 frequency-matched controls, odds ratios (ORs) and corresponding 95% confidence intervals (95%CIs), according to matching variables and relevant confounders. Italy, 2003–2014.

Variable	Cases		Controls		OR (95%CI)[†]
	n	(%)	n	(%)	
Sex					
Men	595	(86.2)	561	(84.4)	
Women	95	(13.8)	104	(15.6)	
Age (years)					
< 60	148	(21.5)	178	(26.8)	
60–64	107	(15.5)	119	(17.9)	
65–69	164	(23.8)	147	(22.1)	
70–74	155	(22.5)	124	(18.7)	
≥75	116	(16.8)	97	(14.6)	
Study centre					
Aviano	242	(35.1)	250	(37.6)	
Milan	241	(34.9)	238	(35.8)	
Naples	129	(18.7)	100	(15.0)	
Catania	78	(11.3)	77	(11.6)	
Education (years)[§]					
< 7	292	(42.3)	273	(41.1)	1[‡]
7–11	224	(32.5)	215	(32.3)	1.10 (0.83–1.45)
≥12	173	(25.1)	177	(26.6)	1.09 (0.80–1.48)
p-value for trend					p = 0.55
Smoking habit[§]					
Never	96	(13.9)	237	(35.6)	1[‡]
Former	310	(44.9)	284	(42.7)	2.82 (2.08–3.82)
Current (cigarettes/day)					
< 20	143	(20.7)	87	(13.1)	4.78 (3.30–6.94)
≥20	132	(19.1)	57	(8.6)	7.49 (4.93–11.37)
p-value for trend					p < 0.01
Abdominal obesity[§]					
No	279	(40.4)	322	(48.4)	1[‡]
Yes	411	(59.6)	342	(51.4)	1.57 (1.23–1.99)
Diabetes mellitus					
No	578	(83.8)	608	(91.4)	1[‡]
Yes	112	(16.2)	57	(8.6)	2.00 (1.40–2.86)
Total energy intake (kcal/day)					
< 1873	178	(25.8)	167	(25.1)	1[‡]
1873 to < 2234	164	(23.8)	167	(25.1)	1.01 (0.73–1.39)
2243 to < 2689	181	(26.2)	165	(24.8)	1.13 (0.81–1.57)
≥2689	167	(24.2)	166	(25.0)	1.01 (0.71–1.42)
p-value for trend					p = 0.81

[†] Estimated by unconditional logistic regression models, adjusting for sex, 5-year age groups (< 60; 60–64; 65–69; 70–74; ≥75 years), study centre, and smoking habit (never; former; current < 20; current ≥20 cigarettes/day).
[§] The sum does not add up to the total because of some missing values.
[‡] Reference category.

2.3. Food groups, cooking methods, and dietary diversity score assessment

Food and recipe items were gathered into 18 food groups (i.e., white meat, red meat, pork, fish, milk/yogurt, cheese, eggs, bread, pasta/rice, wholegrain, vegetable soup, raw vegetables, cooked vegetables, pulses, potatoes, citrus fruit, non-citrus fruit, and dried fruit) according to similarity of nutritional properties (Supplementary Table S1). Food groups were expressed in grams per week by weighing each food (or recipe) consumed for the corresponding serving weight. Methods of cooking meat were assessed based on the following different techniques: boiling, stewing, roasting/grilling, frying/pan-frying, and preserving.

The dietary diversity score (DDS) was computed by summing up the number of different foods or recipes consumed over a week [25]. For the DDS we defined as 'no consumption' a food or a recipe consumed

Table 2

Odds ratios (ORs) and 95% confidence intervals (95%CIs) for bladder cancer risk according to consumption of food groups from animal sources. Italy, 2003–2014.

Food group	Quartile of consumption (g/week)				p-value for trend
	I	II	III	IV	
Total meat	< 685	685 to < 900	900 to < 1153	≥1153	
Ca:Co	155:167	167:167	184:168	184:163	
OR (95%CI)[†]	1[‡]	1.15 (0.82–1.61)	1.33 (0.95–1.88)	1.57 (1.07–2.31)	p = 0.02
White meat	< 200	200 to < 300	300 to < 500	≥500	
Ca:Co	157:161	214:194	192:212	127:98	
OR (95%CI)[†]	1[‡]	1.04 (0.75–1.44)	0.95 (0.68–1.31)	1.55 (1.05–2.27)	p = 0.11
Red meat	< 295	295 to < 455	455 to < 593	≥593	
Ca:Co	182:167	183:167	135:165	190:166	
OR (95%CI)[†]	1[‡]	0.96 (0.70–1.33)	0.80 (0.57–1.13)	1.13 (0.80–1.60)	p = 0.72
Pork	< 125	125 to < 200	200 to < 275	≥275	
Ca:Co	194:195	159:162	153:150	184:158	
OR (95%CI)[†]	1[‡]	0.96 (0.70–1.33)	1.06 (0.76–1.48)	1.19 (0.85–1.67)	p = 0.28
Fish	< 190	190 to < 300	300 to < 380	≥380	
Ca:Co	209:173	187:171	131:155	163:166	
OR (95%CI)[†]	1[‡]	0.88 (0.65–1.20)	0.65 (0.47–0.91)	0.76 (0.54–1.06)	p = 0.03
Milk/yogurt	< 113	113 to < 878	878 to < 1025	≥1 025	
Ca:Co	216:172	207:163	138:166	129:164	
OR (95%CI)[†]	1[‡]	0.88 (0.65–1.20)	0.62 (0.44–0.86)	0.62 (0.44–0.87)	p < 0.01
Cheese	< 170	170 to < 278	278 to < 403	≥403	
Ca:Co	159:167	170:166	175:167	186:165	
OR (95%CI)[†]	1[‡]	1.13 (0.81–1.57)	1.20 (0.86–1.67)	1.22 (0.87–1.72)	p = 0.23
Eggs	< 98	98 to < 163	≥163		
Ca:Co	351:309	242:244	97:112		
OR (95%CI)[†]	1[‡]	0.92 (0.71–1.18)	0.82 (0.56–1.19)		p = 0.27

[†] Estimated by unconditional logistic regression models, adjusting for sex, 5-year age groups (< 60; 60–64; 65–69; 70–74; ≥75 years), study centre, education (< 7; 7–11; ≥12 years), smoking habit (never; former; current < 20; current ≥20 cigarettes/day), abdominal obesity, diabetes mellitus, and total energy intake (kcal/day; in continuous).

[‡] Reference category; Ca, cases; Co, controls.

Table 3

Odds ratios (ORs) and 95% confidence intervals (95%CIs) for bladder cancer risk according to meat cooking methods. Italy, 2003–2014.

Cooking method	Quartile of consumption (g/week)				p-value for trend
	I	II	III	IV	
Boiling	Never	< 175	175 to < 275	≥275	
Ca:Co	207:191	205:176	94:132	184:166	
OR (95%CI)[†]	1[‡]	1.14 (0.83–1.56)	0.63 (0.44–0.91)	1.13 (0.82–1.57)	p = 0.90
Stewing	< 125	125 to < 178	178 to < 243	≥373	
Ca:Co	169:178	165:168	174:162	182:157	
OR (95%CI)[†]	1[‡]	1.03 (0.75–1.43)	1.22 (0.88–1.70)	1.47 (1.03–2.09)	p = 0.03
Roasting	< 248	248 to < 353	353 to < 470	≥470	
Ca:Co	172:172	146:171	174:159	198:163	
OR (95%CI)[†]	1[‡]	0.78 (0.56–1.09)	1.05 (0.76–1.47)	1.41 (1.00–1.99)	p = 0.02
Frying	Never	< 85	85 to < 120	≥120	
Ca:Co	91:97	237:205	156:172	206:191	
OR (95%CI)[†]	1[‡]	1.15 (0.79–1.66)	0.90 (0.61–1.32)	1.10 (0.75–1.61)	p = 0.94
Preserving	< 75	75 to < 125	125 to < 175	≥175	
Ca:Co	175:153	174:186	173:174	168:152	
OR (95%CI)[†]	1[‡]	0.74 (0.54–1.03)	0.77 (0.55–1.07)	0.93 (0.66–1.32)	p = 0.72

[†] Estimated by unconditional logistic regression models, adjusting for sex, 5-year age groups (< 60; 60–64; 65–69; 70–74; ≥75 years), study centre, education (< 7; 7–11; ≥12 years), smoking habit (never; former; current < 20; current ≥20 cigarettes/day), abdominal obesity, diabetes mellitus, and total energy intake (kcal/day; in continuous).

[‡] Reference category; Ca, cases; Co, controls.

less than once per week.

2.4. Statistical analyses

Given that there was no problem of sparse data, odds ratios (ORs) and the corresponding 95%CIs of the association between various dietary aspects and bladder cancer risk were estimated by unconditional logistic regression models [26], which have been reported to increase estimate precision with no loss of validity [27]. To maximise statistical power, dietary variables were categorised in quartiles; regression equations further included terms for study centre, sex, age (< 60; 60–64; 65–69; 70–74; ≥75 years), education (< 7; 7–11; ≥12 years), smoking habit (never; former; current < 20; current ≥20 cigarettes/day), total energy intake (kcal/day; in continuous), history of diabetes mellitus, and abdominal obesity. Abdominal obesity, as a proxy of visceral and subcutaneous fat, was defined as the waist circumference ≥94 cm for men and ≥80 cm for women, according to the International Diabetes Federation guidelines [28]. In addition, body mass index (BMI) ≥30 kg/m^2 was used as a proxy of abdominal obesity in patients with missing values for waist circumference [6].

In evaluating the relationship between DDS and bladder cancer risk, we further adjusted DDS risk estimates for consumption of specific food

Table 4
Odds ratios (ORs) and 95% confidence intervals (95%CIs) for bladder cancer risk according to consumption of food groups from vegetal sources. Italy, 2003–2014.

Food group	Quartile of consumption (g/week)				p-value for trend
	I	II	III	IV	
Cereals	< 1203	1203 to < 1553	1553 to < 2040	≥2040	
Ca:Co	145:168	175:165	206:167	164:165	
OR (95%CI)[†]	1[‡]	1.51 (1.08–2.13)	1.76 (1.24–2.49)	1.53 (1.00–2.33)	p = 0.02
Bread	< 473	473 to < 773	773 to < 1128	≥1128	
Ca:Co	155:167	162:184	182:155	191:159	
OR (95%CI)[†]	1[‡]	1.09 (0.78–1.51)	1.58 (1.12–2.22)	1.61 (1.11–2.34)	p < 0.01
Pasta/rice	< 488	488 to < 595	595 to < 733	≥733	
Ca:Co	177:172	149:164	176:163	188:166	
OR (95%CI)[†]	1[‡]	0.97 (0.70–1.35)	1.22 (0.88–1.69)	1.16 (0.82–1.63)	p = 0.23
Wholegrain	Never	Ever			
Ca:Co	478:422	212:243			
OR (95%CI)[†]	1[‡]	0.80 (0.62–1.03)			
Vegetal soup	< 200	200 to < 350	350 to < 650	≥650	
Ca:Co	199:166	156:164	178:168	157:167	
OR (95%CI)[†]	1[‡]	0.78 (0.56–1.08)	0.85 (0.61–1.18)	0.67 (0.47–0.95)	p = 0.05
Total vegetables	< 386	386 to < 558	558 to < 760	≥760	
Ca:Co	216:167	184:166	149:166	141:166	
OR (95%CI)[†]	1[‡]	0.77 (0.56–1.05)	0.67 (0.47-0.93)	0.62 (0.44-0.88)	p < 0.01
Raw vegs	< 82	82 to < 194	194 to < 366	≥366	
Ca:Co	175:177	204:158	186:171	125:159	
OR (95%CI)[†]	1[‡]	1.33 (0.96–1.84)	1.17 (0.83–1.64)	0.90 (0.61–1.30)	p = 0.52
Cooked vegs	< 197	197 to < 330	330 to < 456	≥456	
Ca:Co	207:169	186:164	149:167	148:165	
OR (95%CI)[†]	1[‡]	0.84 (0.61–1.15)	0.62 (0.45–0.87)	0.65 (0.46–0.91)	p < 0.01
Pulses	< 33	33 to < 64	≥64		
Ca:Co	208:175	189:215	293:275		
OR (95%CI)[†]	1[‡]	0.68 (0.50–0.92)	0.82 (0.60–1.10)		p = 0.22
Potatoes	< 88	88 to < 151	151 to < 204	≥204	
Ca:Co	186:147	182:181	199:206	123:131	
OR (95%CI)[†]	1[‡]	0.76 (0.55–1.05)	0.75 (0.54–1.03)	0.79 (0.54–1.13)	p = 0.16
Total fruit	< 1345	1345 to < 2112	2112 to < 2983	≥2983	
Ca:Co	191:167	190:166	152:166	157:166	
OR (95%CI)[†]	1[‡]	1.12 (0.81–1.53)	0.91 (0.66–1.27)	1.00 (0.71–1.41)	p = 0.71
Citrus fruit	< 188	188 to < 488	488 to < 600	≥600	
Ca:Co	210:186	146:161	167:176	167:142	
OR (95%CI)[†]	1[‡]	0.86 (0.62–1.18)	0.94 (0.69–1.29)	1.22 (0.88–1.70)	p = 0.27
Non-citrus fruit	< 1027	1027 to < 1650	1650 to < 2425	≥2425	
Ca:Co	191:167	202:167	154:166	143:165	
OR (95%CI)[†]	1[‡]	1.08 (0.78–1.48)	0.92 (0.66–1.29)	0.86 (0.60–1.22)	p = 0.30
Dryed fruit	Never	Ever			
Ca:Co	481:420	209:245			
OR (95%CI)[†]	1[‡]	0.86 (0.67–1.10)			

[†] Estimated by unconditional logistic regression models, adjusting for sex, 5-year age groups (< 60; 60–64; 65–69; 70–74; ≥75 years), study centre, education (< 7; 7–11; ≥12 years), smoking habit (never; former; current < 20; current ≥20 cigarettes/day), abdominal obesity, diabetes mellitus, and total energy intake (kcal/day; in continuous).
[‡] Reference category; Ca, cases; Co, controls.

groups (quartiles of servings/week) to disentangle the effect of DDS and food consumption. Test for trend was based on the likelihood ratio test between models with and without the linear term for the variable under consideration.

3. Results

Table 1 shows the distribution of cases and controls according to the matching variables and selected potential confounders, with corresponding ORs. A significant direct association was observed between bladder cancer risk and smoking habits, abdominal obesity, and diabetes mellitus. No association emerged for education level and total energy intake.

Meat consumption was positively associated with bladder cancer risk (p for trend = 0.02), with an OR of 1.57 (95%CI: 1.07–2.31) for an intake of ≥1153 g/week (highest quartile) compared to < 685 g/week (lowest quartile; Table 2). No significant trend in risk emerged for different meat types (i.e., white meat, red meat, and pork), although the ORs for the highest quartile were > 1 for all meat types. Conversely, an inverse association emerged for milk/yogurt consumption (p for trend < 0.01), with a 38% significant reduction in bladder cancer risk (OR = 0.62; 95%CI: 0.44–0.87; Table 2) for a week's intake ≥1025 g (i.e., approximately one serving/day). No association was found for consumption of fish, cheese and eggs.

With reference to methods of cooking meat, a significant increased bladder cancer risk was found for stewing (OR = 1.47; 95%CI: 1.03–2.09 for ≥373 g/week versus < 125 g/week; p for trend = 0.03) and roasting (OR = 1.41; 95%CI: 1.00–1.99 for ≥470 g/week versus < 248 g/week; p for trend = 0.02), whereas no association emerged for boiling, frying, or for preserving (Table 3).

Total cereal consumption was positively associated with the risk of bladder cancer (Table 4). In our study population, almost all cereal intake was due to white bread (including breadsticks, crackers and crisp toasts; average fraction: 51.8%) and pasta and rice (42.4%), whereas wholegrain products were consumed rarely in the Italian population (5.8% of all cereals). Subjects eating ≥1128 g/week of bread showed an elevated risk (OR = 1.61; 95%CI: 1.11–2.34) compared to those eating < 473 g/week (p for trend < 0.01). Notably, people eating wholegrain products have a reduced (though non-significant) risk of bladder cancer compared to non-consumers (OR = 0.80; 95%CI:

Table 5
Odds ratios (ORs) and 95% confidence intervals (95%CIs) for bladder cancer risk according to dietary diversity score. Italy, 2003–2014.

Dietary diversity score	Quartile of consumption (number of foods consumed/week)				p-value for trend
	I	II	III	IV	
Overall	< 14	14 to 16	17 to 19	≥20	
Ca:Co	159:167	170:166	175:167	186:165	
OR (95%CI)[†]	1[‡]	0.97 (0.70–1.35)	0.88 (0.63–1.24)	0.79 (0.54–1.16)	p = 0.19
Total meat	< 4	4 to 5	≥6		
Ca:Co	159:167	170:166	175:167		
OR (95%CI)[†]	1[‡]	1.19 (0.86–1.65)	1.21 (0.81–1.79)		p = 0.38
Milk/yogurt	Never	1	≥2		
Ca:Co	159:167	170:166	175:167		
OR (95%CI)[†]	1[‡]	1.26 (0.69–2.30)	0.99 (0.50–1.95)		p = 0.31
Cereals	< 5	5 to 6	≥7		
Ca:Co	159:167	170:166	175:167		
OR (95%CI)[†]	1[‡]	1.06 (0.81–1.39)	0.78 (0.56–1.09)		p = 0.18
Total vegetables	< 3	3	≥4		
Ca:Co	159:167	170:166	175:167		
OR (95%CI)[†]	1[‡]	0.79 (0.58–1.06)	0.73 (0.52–1.03)		p = 0.06
Total fruit	< 4	4 to 5	≥6		
Ca:Co	159:167	170:166	175:167		
OR (95%CI)[†]	1[‡]	1.13 (0.86–1.49)	1.11 (0.76–1.61)		p = 0.51

[†] Estimated by unconditional logistic regression models, adjusting for sex, 5-year age groups (< 60; 60–64; 65–69; 70–74; ≥75 years), study centre, education (< 7; 7–11; ≥12 years), smoking habit (never; former; current < 20; current ≥20 cigarettes/day), abdominal obesity, diabetes mellitus, specific food group consumption (quartiles of servings/week; when appropriate), and total energy intake (kcal/day; in continuous).
[‡] Reference category; Ca, cases; Co, controls.

0.62–1.03). Vegetable intake, but not fruit intake, was inversely associated with the risk of bladder cancer (p for trend < 0.01), with an OR of 0.62 (95%CI: 0.44–0.88) for a consumption ≥760 g/week compared to < 386 g/week. This association was due mainly to the consumption of cooked vegetables (OR for highest versus lowest quartile = 0.65; 95%CI: 0.46–0.91). Moreover, the association between vegetable consumption and bladder cancer risk was stronger among women (OR = 0.31, 95%CI: 0.12–0.83) than among men (OR = 0.66; 95%CI: 0.45–0.97) (data not shown). Mutual adjustment between food groups did not substantially modify previous risk estimates (data not shown).

There was a suggestion that a diversified diet reduced the risk of bladder cancer, but this trend was not significant (Table 5).

4. Discussion

In this study we found inverse associations between bladder cancer risk and consumption of vegetables and milk/yogurt, whereas we found direct associations between bladder cancer risk and consumption of bread and meat. Moreover, meat roasting and stewing were associated with an increased bladder cancer risk. Results for diet diversity were inconclusive, although our data suggest a possible protective role for a more diversified diet.

Findings from a recent meta-analysis including ten cohort studies showed an overall relative risk (RR) of 0.92 (95%CI: 0.84–1.01) for the highest compared to the lowest vegetable consumption [29]. The pooled data from two prospective studies in the United Kingdom which investigated cancer incidence in vegetarians for 20 cancer sites reported a lower bladder cancer incidence for vegetarians compared to meat eaters (RR = 0.47 95%CI: 0.25–0.89) [30]. In a prospective analysis of 185,885 participants in the multi-ethnic cohort study, vegetable consumption was associated with a reduced bladder cancer risk mainly in women (RR for the highest versus lowest quartiles = 0.49, 95%CI: 0.29–0.83) [31], as in our study. Vegetables provide abundant sources of vitamins and minerals as well as phytochemicals which are known to decrease oxidative stress and inflammation, with a beneficial role in the pathogenesis of cancer [32]. Therefore, the beneficial effect should be more evident for raw vegetables; surprisingly, in our study the inverse association with bladder cancer risk was stronger for cooked vegetables than for raw ones.

The divergent association observed in our study for total cereal (OR = 1.53, 95%CI: 1.00–2.33) and wholegrain (OR = 0.80, 95%CI: 0.62–1.03) consumption could be partially explained by the different glycaemic indexes and glycaemic loads of these foods. Diets with a low glycaemic index/glycaemic load (including diets rich in wholegrain products) have been shown to decrease concentrations of fasting blood glucose, glycosylated proteins, and insulin, and consequently reduce the risk of developing some chronic diseases, including cancer [33,34]. Furthermore, wholegrain products have a higher content of fibre. However, these results should be considered with caution, since wholegrain products were consumed rarely in the Italian population and may rather be a proxy of a healthy lifestyle, confounding the reported association.

Some studies have evaluated the relationship between meat consumption and the risk of bladder cancer [12,13,35–37]. Crippa and colleagues [35] conducted a meta-analysis of five cohort studies and eight case–control studies published up to 2016, showing an overall RR of 1.22 (95%CI: 1.05–1.41) for an increment of 100 g/day of red meat. However, there was heterogeneity between study designs, with pooled RRs of 1.01 (95%CI: 0.97–1.06) in cohort studies and 1.51 (95%CI 1.13–2.02) in case–control studies. Among studies assessing the role of cooking techniques, a case–control study conducted in the US [38] showed an increased bladder cancer risk for the highest quartile of heterocyclic amine (HCA) intake compared with the lowest quartile (OR = 3.32; 95%CI: 1.41–2.68). Conversely, three other studies did not find any association for cooking techniques [13,36,37]. Chicken and red meat are rich in amino acids, which are natural precursors of HCAs, particularly PhIP and MeIQx [39]. These HCAs formed during food preparation—especially when meat is cooked at higher temperatures (e.g. roasting) or for prolonged times (e.g. stewing)—can facilitate DNA damage [40] and promote cancer risk [41]. However, the lack of information on 'doneness' should be accounted among the study limitations, since it can greatly impact HCA formation.

As for other hospital-based case–control studies, the present study may suffer from information, recall, and selection biases. However, direct interview of cases and controls by the same trained interviewers and under similar conditions (a hospital setting) should have minimised information bias. Moreover, bias in recalling of dietary habits should be negligible, as the awareness of the dietary hypothesis for bladder cancer is limited, particularly in our study population. Dietary habits of hospital controls may be unrepresentative of those of the general population. However, we excluded from the control group patients admitted for any condition related to long-term dietary modifications.

Within-person variability over the study period may also be a source of information bias. However, dietary habits were quite stable in the Italian population, and patients were asked to report any relevant dietary change occurring during their life. Selection bias was limited by the nearly complete participation of the identified cases and controls, which was favoured by the interview during hospital stay. Furthermore, the use of a validated and reproducible FFQ strengthened our findings.

In conclusion, our findings consolidate the concept of a role for diet in bladder cancer aetiology. In particular, vegetable and milk/yogurt consumption reduced bladder cancer risk, while meat increased the risk of bladder cancer. Further researches are needed to clarify the role of meat and cooking techniques in bladder carcinogenesis.

Authorship contributions

C. La Vecchia, E. Negri, and D. Serraino have carried out the study design. C. Bosetti, M. Libra, and M. Montella have parcipated in the data collection. M. Di Maso and J. Polesel have performed statistical analyses and drafted the original version of the manuscript. M. Ferraroni and F. Turati have revised the original version of manuscript. All authors have critically reviewed and approved the final version of the manuscript.

Declaration of Competing Interest

None declared.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2019.101595.

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