

UCLA

UCLA Previously Published Works

Title

Fruits and vegetables intake and bladder cancer risk: a pooled analysis from 11 case–control studies in the BLadder cancer Epidemiology and Nutritional Determinants (BLEND) consortium

Permalink

<https://escholarship.org/uc/item/2wd6j9f7>

Journal

European Journal of Nutrition, 63(7)

ISSN

1436-6207

Authors

Boot, Iris WA

Wesselius, Anke

Jochems, Sylvia HJ

et al.

Publication Date

2024-10-01

DOI

10.1007/s00394-024-03436-5

Peer reviewed



Fruits and vegetables intake and bladder cancer risk: a pooled analysis from 11 case–control studies in the BLadder cancer Epidemiology and Nutritional Determinants (BLEND) consortium

Iris W. A. Boot^{1,2,3} · Anke Wesselius¹ · Sylvia H. J. Jochems¹ · Evan Y. W. Yu^{2,3,4} · Cristina Bosetti⁵ · Martina Taborelli⁶ · Stefano Porru^{7,8} · Angela Carta⁸ · Klaus Golka⁹ · Xuejuan Jiang^{10,11} · Mariana C. Stern¹⁰ · Eliane Kellen¹² · Hermann Pohlabein¹³ · Li Tang¹⁴ · Margaret R. Karagas¹⁵ · Zuo-Feng Zhang¹⁶ · Jack A. Taylor¹⁷ · Carlo La Vecchia¹⁸ · Maurice P. Zeegers¹

Received: 19 January 2024 / Accepted: 15 May 2024 / Published online: 5 June 2024
© The Author(s) 2024

Abstract

Purpose High consumption of fruits and vegetables decrease the risk of bladder cancer (BC). The evidence of specific fruits and vegetables and the BC risk is still limited.

Methods Fruit and vegetable consumptions in relation to BC risk was examined by pooling individual participant data from case–control studies. Unconditional logistic regression was used to estimate study-specific odds ratio's (ORs) with 95% confidence intervals (CIs) and combined using a random-effects model for intakes of total fruits, total vegetables, and subgroups of fruits and vegetables.

Results A total of 11 case–control studies were included, comprising 5637 BC cases and 10,504 controls. Overall, participants with the highest intakes versus the lowest intakes of fruits in total (OR 0.79; 95% CI 0.68–0.91), citrus fruits (OR 0.81; 95% CI 0.65–0.98), pome fruits (OR 0.76; 95% CI 0.65–0.87), and tropical fruits (OR 0.84; 95% CI 0.73–0.94) reduced the BC risk. Greater consumption of vegetables in total, and specifically shoot vegetables, was associated with decreased BC risk (OR 0.82; 95% CI 0.68–0.96 and OR 0.87; 95% CI 0.78–0.96, respectively). Substantial heterogeneity was observed for the associations between citrus fruits and total vegetables and BC risk.

Conclusion This comprehensive study provides compelling evidence that the consumption of fruits overall, citrus fruits, pome fruits and tropical fruits reduce the BC risk. Besides, evidence was found for an inverse association between total vegetables and shoot vegetables intake.

Keywords Bladder cancer · Nutritional oncology · Pooled case control study · Fruits · Vegetables

Introduction

Consumption of fruits and vegetables is an important part of a healthy diet and has been linked to a reduced risk of cancer [1]. A report on diet and bladder cancer (BC) from the *WCRF Continuous Update Project* concluded that high intakes of fruit and vegetables could decrease the BC risk [2]. In addition, results of a large systematic review suggested that the consumption of citrus fruits and cruciferous vegetables decreases BC risk [3], and another review suggested that a diet rich in vegetables and fruits might be protective against BC [4].

Previous studies have often lacked adequate statistical power to detect associations between dietary factors and BC risk. Aside from total fruit and total vegetable consumption, associations between subgroups of fruits and vegetables and BC risk have been reported sporadically and may be subject to publication bias. As fruits and vegetables are heterogeneous with respect to phytochemical content [5], associations with BC risk may differ between types of fruits and vegetables. The use of individual data from multiple case–control studies could substantially increase statistical power, and covariates can be standardized across studies.

The aim of this large-scale pooled study was to investigate the association between total fruit and total vegetable consumption and specific subgroups of fruits and vegetables and BC risk using data of 5,648 BC cases and 10,517

Extended author information available on the last page of the article

controls from 11 studies which were included in the Bladder cancer Epidemiology and Nutritional Determinants (BLEND) consortium.

Methods

Study population

Data were analyzed from the BLEND study. BLEND is a large international nutritional consortium on BC, which includes nineteen case–control studies originating from countries all over the world [6]. Eleven of the nineteen case–control studies had sufficient information (i.e., data on usual dietary intake, method of dietary assessment, geographical region, ethnicity, gender, smoking status, disease status, age at BC diagnosis and/or age at enrollment of the study) to be eligible for inclusion in our study on the influence of total fruit and total vegetable consumption and specific subgroups of fruits and vegetables on BC risk. Studies originated from the USA, Belgium, Sweden, Italy, Canada and China. Each participating study has been approved by a local ethics committee. Informed consent was obtained from all individual participants included in each study.

Data collection

Details on the methodology of the BLEND consortium have been described elsewhere [6]. Briefly, BC cases were ascertained by using medical record review or linkage with a cancer registry. Both non-muscle invasive BC (NMIBC) and muscle invasive BC (MIBC) were considered as outcomes.

For each study, participants were asked to report the frequency of fruit and vegetable items consumed during the preceding one or two years before study enrollment. All studies made use of a validated self-administered food frequency questionnaire (FFQ) or a questionnaire administered by a trained interviewer regarding the frequency of fruit and vegetable consumption. Summary details of the FFQs used in the included studies can be found in Appendix 1, Table 5. Total fruit consumption was computed as the sum of all fruit items in each study, and total vegetable consumption as the sum of all vegetable items provided. The following subgroups of fruits were defined: citrus fruits, pome fruits, soft fruits, stone fruits, tropical fruits, fruit mixtures, and fruit products (Table 1). For vegetables, the defined subgroups were: leaf vegetables, brassica, stalk vegetables, shoot vegetables, tubers, onion-family vegetables, root vegetables, fruit vegetables, pod seeds, fungi, seaweeds, vegetables mixtures, and vegetables products (Table 1). No analyses were performed for fruit mixtures, fruit products, onion-family vegetables, root vegetables, fruit vegetables, pod seeds, fungi, seaweeds, vegetable mixtures, or vegetable products because

of the limited number of participants consuming fruits or vegetables from these subgroups.

Statistical analysis

Participants who reported a history of cancer other than nonmelanoma skin cancer prior to study entry, or had missing data on age at study entry, gender, smoking status, pack years, or fruit and vegetable consumption, were excluded from the analyses. In the analyses, fruit and vegetable consumption were categorized into three consumption levels (low intakes/moderate intakes/high intakes), corresponding to study-specific marginal tertiles. The investigated fruit subgroups (citrus fruits, pome fruits, soft fruits, stone fruits, and tropical fruits) and vegetable subgroups (leaf vegetables, brassica, stalk vegetables, shoot vegetables, and tubers) were also modeled as study-specific marginal tertiles. Although the tertile approach does not take into account true differences in the distribution of population intakes across studies, reported intakes may differ across studies based on country-specific portions sizes and differences in FFQs used, and is therefore our preferred approach [6].

The analytic approach was a two-stage process. First, study-specific odds ratios (ORs) were calculated using unconditional logistic regression models (with low consumption levels as the reference group). The majority of the included case–control studies matched on age and gender only. Although matched methods (e.g., from conditional logistic regression) are robust to matching distortion, unmatched methods like unconditional logistic regression appear to be viable options for loose-matching data, e.g., data matched on a small number of demographic variables like age and gender. After that, the estimates were pooled using a random effects meta-analysis approach to calculate an overall estimate and 95% confidence interval (CI). Adjustments were made for the following potential confounders: gender (male, female), age at study entry (<45 years, 45–49 years, 50–54 years, 55–59 years, 60–64 years, 65–69 years, 70–74 years, >75 years), smoking status (never smoker/former smoker/current smoker), and pack years (<9 years, 9–17 years, 18–30 years, 31–46 years, >47 years). Interactions between age and total fruit and vegetable consumption, gender and total fruit and vegetable consumption, and smoking status and total fruit and vegetable consumption were tested and showed no significant interactions. Nonetheless, besides the overall analysis, subgroup analyses were performed on the two main study-specific matching factors gender and age, as recommended by the study of Smith-Warner et al. [7]. Small study effects were analyzed by funnel plots. A sensitivity analysis was performed, leaving out the only study conducted in Asia. All statistical analyses were performed using Stata software version 14. A two-sided p value < 0.05 was considered statistically significant.

Table 1 Characteristics of vegetable subgroups investigated in the pooled case–control analyses

Subgroups of fruits	
Citrus fruits	Lemons, oranges, tangerines, grapefruits, pomelos, limes, kumquats
Soft fruits	Strawberries, raspberries, white grapes, black grapes, loganberries, blackberries, dewberries, cloudberrries, gooseberries, black currants, red currants, white currants, cranberries, bilberries, cowberries, blueberries, elderberries, rowanberries, physalis, mulberries, bearberries, sea buckthorns
Stone fruits	Apricots, peaches, nectarines, plums, damsons, mirabelles, greengages, sweet cherries, sour cherries, chickasaws, susinas, sloes, dates, lychees, persimmons, barbados cherries
Pome fruits	Apples, pears, quinces, medlars, and loquats
Tropical fruits	Bananas, pineapples, kiwi fruits, (water)melons, figs, mangos, pomegranates, passion fruits, cashew fruits, guavas, papayas, rose hips, sapodillas, carambolas, durians, jack fruits, chayotes, rambutans, tamarinds
Fruit products	Dried mixed fruits, mixed peels, glace cherries, crystallized pineapple, apple sauce, cranberry sauce
Fruit mixtures	Fruit cocktail, fruit salad
Subgroups of vegetables	
Leaf vegetables	Endive, lettuce, lamb's lettuce, swiss chard, spinach, garden orache, cress seedling, mustard seedling, land cress, watercress, vine leaf, dandelion leaf, nettle, sorrel, purslane, parsley
Brassica	Broccoli, cauliflower, cabbage, red cabbage, Chinese cabbage, brussels sprouts, turnip tops, kohlrabi, curly kale
Stalk vegetables	Celery, fennel, sea kale, rhubarb
Shoot vegetables	Asparagus, chicory, globe artichoke, bamboo shoot, palm heart
Tubers	New potato, main crop potato, Jerusalem artichoke, sweet potato, yam, cassava, taro
Onion-family vegetables	Onion, spring onion, shallot, leek, garlic, chives
Root vegetables	Carrot, salsify, celeriac, parsnip, turnip, swede, radish, beetroot, parsley root
Fruit vegetables	Tomato (raw and cooked), aubergine, sweet pepper, chilli pepper, cucumber, courgette, cucurbita, other gourds, ackee, breadfruit, matoki, plantain, avocado, olive
Pod seeds	Pea, broad bean, wax bean, French bean, runner bean, sweet corn, okra
Fungi	Cultivated mushroom, field mushroom, honey mushroom, boletus, truffle, morel, cantharelle, orange agaric, oyster mushroom, shitake mushroom, straw mushroom
Seaweeds	Irish miss, kombu, laver, wakame
Vegetable mixes	Mixed vegetables, mustard and cress, pot herbs
Vegetable products	Mushy peas, garlic puree, tomato puree, vegetable puree, pickled gherkins, pickled onion, pickled red cabbage, sauerkraut

Results

Of the nineteen case–control studies, six studies were excluded for providing no data on fruit or vegetable consumption, and two studies were excluded for providing no data on portion sizes. The eleven included case–control studies [8–18] originated from Belgium, Italy, Sweden, China, Canada, and the USA. In total, out of 17,012 eligible participants, 871 were excluded for having missing data on fruit or vegetable intakes ($n = 595$), age at study entry ($n = 8$), or pack years ($n = 268$) (Fig. 1).

Baseline characteristics of the included studies are presented in Table 2. A total of 5637 BC cases and 10,504 controls were analyzed. Most of these included participants were male (68%) and Caucasian (89%). The mean age for BC was 60 years across all studies. Even though all studies made use of an FFQ to measure usual fruit and vegetable consumption (over the preceding one or two years before study enrollment), the number of fruit and

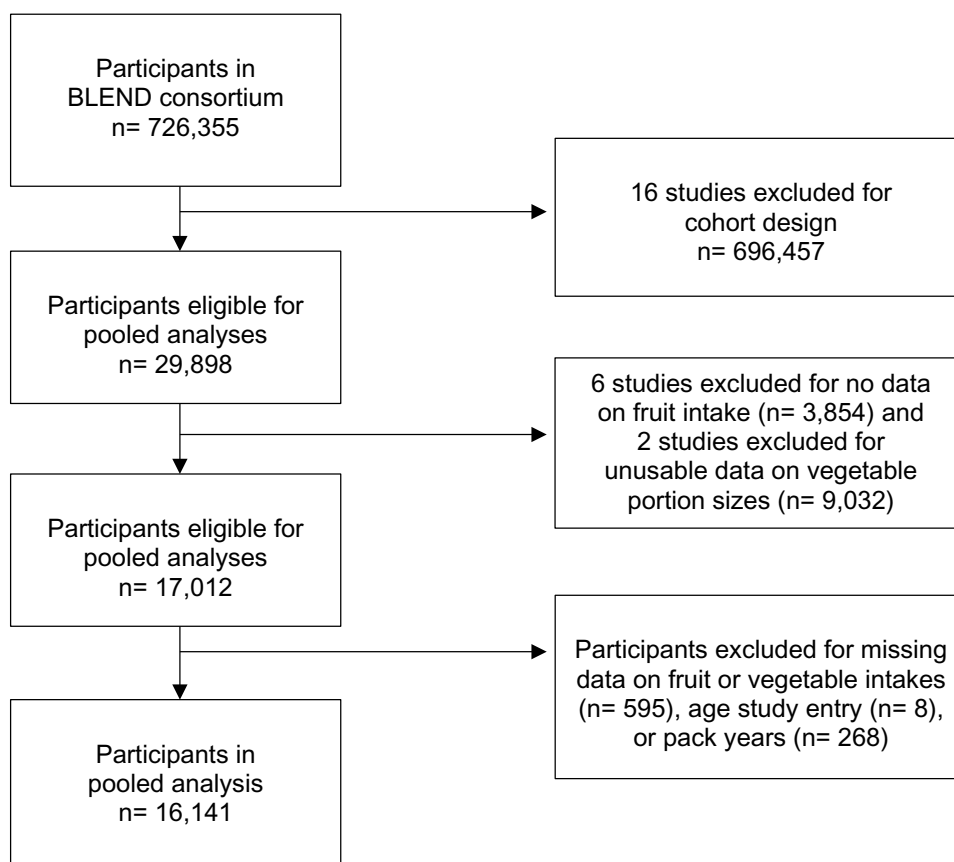
vegetable items described in each questionnaire varied widely.

Total fruits

Among the eleven included studies, nine demonstrated a trend towards reduced BC risk with higher intake of total fruit, although the association was not always statistically significant (Table 3, Fig. 2). Remarkably, one study reported a non-significant increased risk (Table 3). However, upon pooled analysis, a reduction in BC risk associated with higher total fruit intake was observed. In the overall pooled analysis, greater intakes of fruit showed a reduced BC risk compared to the lowest intakes of fruit (OR 0.79; 95% CI 0.68–0.91) (Table 3). The tests for heterogeneity showed moderate heterogeneity for the association between total fruit and BC ($I^2 = 42.8\%$).

In the subgroup analysis on gender, similar results were observed in both men and women, showing a pooled decreased BC risk among those consuming the highest

Fig. 1 Flow diagram of exclusion criteria for participants included in the pooled case–control analyses on fruit and vegetable intakes



intakes of fruit ($OR_{men} = 0.83$; 95% CI 0.71–0.95) (Table 4), and $OR_{women} = 0.60$; 95% CI 0.40–0.80 (Table 5)). Whilst the heterogeneity among men for the might not be considerable ($I^2 = 25.7\%$), the heterogeneity among women may represent moderate heterogeneity ($I^2 = 43.3\%$) (Appendix 2, Tables 6, 7).

Similarly, when analyzing the data according to age (i.e., 60 years and under), consistent results were observed. In the overall pooled analysis, participants younger than 60 years of age with high fruit consumption exhibited a significant decrease in BC risk (OR 0.76; 95% CI 0.64–0.88), with no considerable statistical heterogeneity observed in this group ($I^2 = 0.0\%$) (Appendix 3, Table 10). Likewise, a decreased BC risk was observed in participants 60 years or older consuming the highest intakes of fruit (OR 0.80; 95% CI 0.69–0.91), with negligible heterogeneity for this association ($I^2 = 5.5\%$) (Appendix 3, Table 11). Additionally, the sensitivity analysis, excluding the Chinese study [12], yielded similar results compared to the overall analysis (OR 0.83; 95% CI 0.72–0.93).

Citrus fruits, pome fruits, soft fruits, stone fruits and tropical fruits

No associations between high consumption of soft fruits or stone fruits and BC risk were found (Table 3). Notably, a trend indicating a lower BC risk was observed for soft fruits in four out of the five studies (Table 3), with the exception of the Stockholm case–control study, where an increased BC risk was observed. For citrus fruits, an overall decreased BC risk was noted with high consumption (OR 0.81; 95% CI 0.65–0.98). Interestingly, a similar trend of lower BC risk for citrus fruits was evident in eight out of the ten studies (Table 3), except for the Belgian case–control study on BC and the Stockholm case–control study, which reported an increased BC risk. However, the overall decreased BC risk results for citrus fruit revealed considerable heterogeneity ($I^2 = 66.2$). Similar patterns were observed in the stratified analysis by gender and age (i.e., > 60 years and under) (Appendix 2, Tables 6, 7, Appendix 3, Tables 10, 11). Among women participants and participants aged 60 years or more, an overall decreased BC risk was observed with high consumption of citrus fruits (OR 0.56; 95% CI 0.32–0.80, and OR 0.80; 95% CI 0.62–0.99, respectively). However, both analyses showed considerable heterogeneity ($I^2 = 62.5\%$, and $I^2 = 53.2\%$, respectively). Conversely,

Table 2 Characteristics of the 11 eligible case–control studies according to disease status, gender, age, and smoking status

Country	Los Angeles BC ca–co study		Roswell Park Cancer Institute		Belgian ca–co study on BC		Stockholm ca–co study		New Hampshire BC study on BC		Italian ca–co study on BC	
	USA	Population based	USA	Population based	Belgium	Population based	Sweden	Population based	USA	Population based	Italy	Hospital based
Case-control study type	USA	Population based	USA	Population based	Belgium	Population based	Sweden	Population based	USA	Population based	Italy	Hospital based
Number of food items asked	49		44		788		188		121		21	
Total participants	No. ^a	%	No. ^a	%	No. ^a	%	No. ^a	%	No. ^a	%	No. ^a	%
Cases	3124	100	862	100	576	100	739	100	567	100	1696	100
Controls	1603	51.31	213	24.71	194	33.68	238	32.21	331	32.21	682	40.21
Men	1521	48.69	649	75.29	382	66.32	501	67.79	236	67.79	1014	59.79
Women	2451	78.46	650	75.41	394	68.40	415	56.16	380	56.16	1297	76.47
Age	673	21.54	212	24.59	182	31.60	324	43.84	187	43.84	399	23.53
<45	374	11.97	46	5.33	3	0.52	0	0	44	0	101	5.96
45–49	331	10.60	34	3.94	8	1.39	0	0	30	0	117	6.90
50–54	548	17.54	67	7.77	71	12.33	39	5.28	49	5.28	192	11.32
55–59	884	28.30	109	12.65	102	17.71	79	10.69	85	10.69	275	16.21
60–64	887	28.39	153	17.75	110	19.10	114	15.43	85	15.43	355	20.93
65–69	100	3.20	175	20.30	97	16.84	172	23.27	143	23.27	344	20.28
70–74	0	0	162	18.79	77	13.37	263	35.59	131	35.59	224	13.21
>75	0	0	116	13.46	108	18.75	72	9.74	0	9.74	88	5.19
Smoking status												
Never smoker	798	25.54	366	42.46	190	32.99	261	35.32	154	35.32	512	30.19
Former smoker	1100	35.21	313	36.31	285	49.48	240	32.48	268	32.48	525	30.40
Current smoker	1226	39.24	183	21.23	101	17.53	238	32.21	145	32.21	672	39.62
	Brescia BC study				NESCC				Molecular epidemiology of BC			
	Italy		Canada		China		USA		Italy		Italy	
Case-control study type	Hospital based		Population based		Hospital based		Hospital based		Hospital based		Hospital based	
Number of food items asked	40		69		52		90		77		77	
Total participants	No. ^b	%	No. ^b	%	No. ^b	%	No. ^b	%	No. ^b	%	No. ^b	%
Cases	390	100	5580	100	943	100	378	100	1286	100	1286	100
Controls	185	47.44	884	15.84	479	50.80	180	47.62	648	47.62	648	50.39
Men	205	52.56	4696	84.16	464	49.20	198	52.38	638	52.38	638	49.61
Women	390	100	2923	52.38	750	79.53	302	79.89	1096	79.89	1096	85.23
Age	0	0	2657	47.62	193	20.47	76	20.11	190	20.11	190	14.77
<45	29	7.44	970	17.38	91	9.65	108	28.57	47	28.57	47	3.65
45–49	15	3.85	473	8.48	37	3.92	38	10.05	40	10.05	40	3.11

Table 2 (continued)

	Brescia BC study	NESCC	South and East China ca-co study	Molecular epidemiology of BC	Italian ca-co study
50–54	30	478	8.57	36	93
55–59	48	568	10.18	36	132
60–64	75	820	14.70	37	208
65–69	70	1082	19.39	62	295
70–74	74	1111	19.91	25	265
> 75	49	78	1.40	36	206
Smoking status					
Never smoker	65	2073	37.15	139	328
Former smoker	176	2353	42.17	194	562
Current smoker	149	1161	20.81	45	400

^a As a result of exclusion criteria, the baseline cohort size and number of cases included in the pooled analyses may differ from original study-specific publications

^b As a result of exclusion criteria, the baseline case–control size and number of cases included in the pooled analyses may differ from original study-specific publications

among participants younger than 60 years, an association between the highest intakes of citrus fruits and BC risk was observed (OR 0.77; 95% CI 0.64–0.91) with no considerable statistical heterogeneity ($I^2 = 0.0\%$). In men, no association was found between greater intakes of citrus fruits and BC risk (Appendix 2, Table 6).

Overall, greater consumption of pome fruits was associated with a decreased BC risk (OR 0.76; 95% CI 0.65–0.87) and statistical heterogeneity was not considerable ($I^2 = 0.0\%$). In the subgroup analyses, pome fruit consumption (highest *versus* lowest intakes) was associated with a lower BC risk in men (OR 0.77, 95% CI 0.58–0.97), women (OR 0.58, 95% CI 0.42–0.73), < 60 years (OR 0.52, 95% CI 0.31–0.72), and ≥ 60 years (OR 0.85, 95% CI 0.71–0.99), with low to moderate heterogeneity ($I^2 = 40.2\%$, $I^2 = 0.0\%$, $I^2 = 15.3\%$, and $I^2 = 0.0$, respectively) (Appendix 2, Tables 6, 7, Appendix 3, Tables 10, 11).

High consumption of tropical fruits was associated with a decreased BC risk in the overall analysis (OR 0.84; 95% CI 0.73–0.94, $I^2 = 20.5\%$). Again, it should be noted that a trend towards a decreased risk was shown in seven out of the nine studies, while the New Hampshire and Molecular epidemiology of BC studies showed a trend towards an increased BC risk. In the subgroup analyses on age, both age groups (< 60 and ≥ 60 years) showed associations between the highest intakes of tropical fruits and BC risk (OR 0.84; 95% CI 0.70–0.98 and OR 0.83; 95% CI 0.72–0.95, respectively) and no heterogeneity was observed for these associations (Appendix 3, Tables 10 and 11).

Total vegetables

Although high total vegetable consumption was associated with BC risk (OR 0.82; 95% CI 0.70–0.94), heterogeneity was observed ($I^2 = 52.9\%$) (Table 4, Fig. 3). In men, the highest intakes of total vegetables were associated with a decreased BC risk with no considerable heterogeneity (OR 0.80; 95% CI 0.71–0.88, $I^2 = 1.0\%$) (Appendix 2, Table 8). Similar results were found for participants ≥ 60 years (OR 0.81; 95% CI 0.71–0.91, $I^2 = 0.0\%$) (Appendix 3, Table 13). Greater intakes of total vegetables among participants < 60 years were significantly associated with a decreased BC risk (OR 0.70; 95% CI 0.52–0.88). However, substantial heterogeneity was observed for this association ($I^2 = 47.8\%$) (Appendix 2, Table 3). The sensitivity analysis did not change the result (OR 0.82; 95% CI 0.69–0.95).

Leaf vegetables, brassica, stalk vegetables, shoot vegetables, and tubers

No associations between high consumptions of brassica, stalk vegetables, and tubers, and BC risk were observed (Table 4). Although subject to substantial heterogeneity,

Table 3 Odds ratios of bladder cancer by total fruit intake for all participants

	Los Angeles BC ca-co study	Roswell Park Cancer Institute	Belgian ca-co study on BC	Stockholm ca-co study	New Hampshire BC study	Italian ca-co study on BC	Brescia BC study	NESCC	South and East China ca-co study	Molecular epidemiology of BC	Italian ca-co study	Pooled estimate	Test for heterogeneity
Total fruits													
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	0.97 (0.81–1.16)	0.79 (0.53–1.18)	0.78 (0.49–1.24)	0.88 (0.59–1.32)	1.15 (0.74–1.77)	1.16 (0.94–1.43)	0.84 (0.50–1.41)	0.82 (0.68–0.98)	0.79 (0.57–1.08)	0.85 (0.41–1.76)	1.13 (0.85–1.50)	0.91 (0.83–0.99)	I ² =4.2%, p=0.403
Q3	0.87 (0.73–1.05)	0.77 (0.51–1.17)	0.51 (0.31–0.83)	0.88 (0.58–1.34)	1.01 (0.65–1.57)	0.87 (0.52–1.47)	1.41 (0.85–2.35)	0.84 (0.69–1.01)	0.56 (0.41–0.78)	0.89 (0.42–1.88)	0.93 (0.70–1.23)	0.79 (0.68–0.91)	I ² =42.8%, p=0.065
Citrus fruits													
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	0.97 (0.81–1.16)	0.59 (0.40–0.85)	1.04 (0.66–1.66)	1.02 (0.70–1.49)	0.93 (0.60–1.44)	1.02 (0.70–1.49)	0.81 (0.49–1.34)	0.97 (0.82–1.14)	0.78 (0.54–1.13)	0.59 (0.26–1.33)	0.98 (0.76–1.26)	0.88 (0.78–0.99)	I ² =25.1%, p=0.213
Q3	0.85 (0.71–1.02)	0.61 (0.39–0.96)	0.72 (0.45–1.16)	0.75 (0.46–1.21)	0.96 (0.62–1.50)	0.87 (0.52–1.47)	1.06 (0.64–1.77)	1.03 (0.84–1.27)	0.52 (0.38–0.72)	0.46 (0.18–1.14)	1.56 (1.09–2.23)	0.81 (0.65–0.98)	I ² =66.2%, p=0.002
Soft fruits													
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	Ref	0.64 (0.42–0.97)	Ref	1.12 (0.62–2.03)	0.62 (0.41–0.93)	Ref	0.99 (0.59–1.63)	Ref	0.71 (0.52–0.96)	Ref	0.96 (0.73–1.27)	0.79 (0.63–0.96)	I ² =26.1%, p=0.247
Q3	Ref	1.00 (0.68–1.48)	Ref	1.43 (0.98–2.08)	1.44 (0.87–2.36)	Ref	2.08 (1.22–3.55)	Ref	0.54 (0.39–0.75)	Ref	1.01 (0.75–1.35)	1.14 (0.69–1.60)	I ² =81.5%, p=0.000
Stone fruits													
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	Ref	0.64 (0.42–0.97)	Ref	0.78 (0.54–1.11)	1.08 (0.70–1.65)	Ref	1.67 (1.00–2.80)	Ref	1.30 (1.01–1.67)	Ref	1.30 (1.01–1.67)	1.05 (0.77–1.33)	I ² =71.2%, p=0.004
Q3	Ref	1.00 (0.68–1.48)	Ref	0.71 (0.42–1.19)	0.95 (0.61–1.48)	Ref	1.66 (1.00–2.75)	Ref	0.46 (0.35–0.62)	Ref	1.27 (0.90–1.79)	0.91 (0.58–1.23)	I ² =78.8%, p=0.000
Pome fruits													
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	Ref	0.92 (0.64–1.31)	Ref	0.82 (0.55–1.21)	1.32 (0.77–2.28)	Ref	1.41 (0.90–2.23)	Ref	0.90 (0.76–1.08)	Ref	0.94 (0.71–1.23)	0.90 (0.74–1.06)	I ² =39.6%, p=0.128
Q3	Ref	0.67 (0.39–1.14)	Ref	0.90 (0.59–1.38)	1.03 (0.69–1.54)	Ref	0.74 (0.32–1.70)	Ref	0.76 (0.62–0.93)	Ref	0.80 (0.59–1.08)	0.76 (0.65–0.87)	I ² =0.0%, p=0.517
Tropical fruits													
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	1.15 (0.96–1.38)	0.98 (0.66–1.43)	Ref	1.00 (0.67–1.49)	0.88 (0.56–1.36)	Ref	1.30 (0.77–2.19)	Ref	0.72 (0.54–0.96)	Ref	1.15 (0.87–1.53)	0.98 (0.86–1.10)	I ² =26.8%, p=0.205
Q3	0.97 (0.81–1.16)	0.90 (0.59–1.40)	Ref	0.91 (0.61–1.37)	1.06 (0.69–1.64)	Ref	0.99 (0.61–1.62)	Ref	0.56 (0.37–0.83)	Ref	0.80 (0.60–1.06)	0.84 (0.73–0.94)	I ² =20.5%, p=0.261

Adjusted for gender, age at study entry (<45 years, 45–49 years, 50–54 years, 55–59 years, 60–64 years, 65–69 years, 70–74 years, >75 years), smoking status (current smoker/former smoker/never smoker), and pack years (<9 years, 9–17 years, 18–30 years, 31–46 years, >47 years)

associations were found for the overall high intake of leaf vegetables and decreased BC risk (OR 0.82; 95% CI 0.68–0.96). This trend was observed for nine out of the eleven studies, while the South and East China ca-co study and NESCC study showed a trend towards an increased BC risk (Table 4).

High intakes of shoot vegetables significantly decreased the BC risk with no observed substantial heterogeneity (OR 0.87; 95% CI 0.78–0.96, $I^2=0.0\%$) (Table 4). In the subgroup analyses, significant associations for leaf vegetables (OR 0.70; 95% CI 0.56–0.84) and shoot vegetables (OR 0.83; 95% CI 0.68–0.97) were found in participants < 60 years with no substantial heterogeneity ($I^2=20.0\%$, and $I^2=0.0\%$, respectively) (Appendix 3, Table 12). Although associations were found for leaf vegetables and BC risk in men, women, and participants ≥ 60 years, substantial heterogeneity was observed for these associations (Appendix 2, Tables 8, 9, Appendix 3, Table 13).

Discussion

In this large pooled analysis of eleven case-control studies, comprising 5637 cases and 10,504 controls, significant inverse associations were found between high fruit and vegetable consumption and BC risk. There were inverse associations between total fruit, citrus fruit, pome fruit, and tropical fruit consumption and BC risk. No associations were found for high consumption of soft fruits or stone fruits. For vegetable consumption, inverse associations were found between total vegetable, leaf vegetable, and shoot vegetable consumption and a BC risk. Brassica, stalk vegetables, and tubers were not associated with BC risk.

It seems plausible that substances in fruits and vegetables including minerals, phytochemicals, and antioxidant nutrients, have potentially anticarcinogenic properties to protect against the development of cancer [1, 19]. Throughout Europe and the USA, apples and pears are the most consumed pome fruits. Apples contain a wide range of phytochemicals which have been found to have strong antioxidant properties and the ability to inhibit cancer cell proliferation [20]. Hence, results from an Italian case-control study and from the EPIC study, which included data from ten European countries, confirm that greater consumption of apples and pears decreases the BC risk (OR 0.63; 95% CI 0.39–0.99, and OR 0.90; 95% CI 0.82–0.98, respectively) [21, 22]. In addition, scientific evidence suggests that vitamin C, an essential nutrient abundant in citrus fruits, exerts anticancer effects in the bladder through diverse pathways. These include a malignancy-inhibiting shift in the transcriptome, as well as elevating levels of 5-hydroxymethylcytosine [23].

Brassica vegetables also contain high levels of phytochemicals, such as glucosinolates and isothiocyanates, and

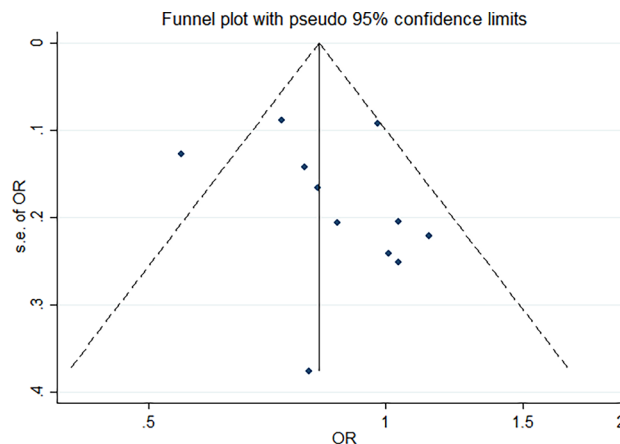


Fig. 2 Funnel plot of overall fruit analyses results

are therefore expected to lower the BC risk [19, 24]. This, however, was not confirmed in this study. Leafy vegetables contain high concentrations of carotenoids that could potentially protect against the damage to DNA by scouring free radicals [25]. Hence, results of a meta-analysis indicated that per 0.2 serving increment of daily green leafy vegetable consumption, the BC risk decreases with 2% [26]. We observed evidence of an inverse association between consumption of leafy vegetables and BC risk, which is consistent with these potential biological mechanisms.

Although no previous studies investigated specifically the role of shoot vegetables or tropical fruits in BC risk, these vegetables and fruits contain a wide range of carotenoids, folates, vitamins, and carotene, which may offer protection against the development of BC [27].

In line with our research a meta-analysis conducted in East Asians showed an inverse association between total fruit intake and BC risk [23]. Furthermore, within our BLEND study investigating fruit intake and BC risk among thirteen cohort studies, an inverse association between fruit intake and BC risk was found in women, but not in men. Nor was an association found for any fruit subgroup [28]. These null associations were confirmed in a Japanese cohort study including 1,287,514 person-years of follow-up. In addition, a null association was also found for total vegetable intake and any subgroup vegetable [29]. These observed differences might be due to the difference in study design. Although both case-control and cohort studies are subject to (a different form of) selection bias, and other methodological limitations, such as measurement error, there is an important methodological difference between these different study types. While in case-control studies, the assessment of lifestyle occurs after diagnosis, in cohort studies, the assessment of lifestyle occurs prior to diagnosis. It is therefore thought that case-control studies are more prone to recall bias and provide a lower certainty of evidence than cohort

Table 4 Odds ratios of bladder cancer by total vegetable intake for all participants

	Los Angeles BC ca-co study	Roswell Park Cancer Institute	Belgian ca-co study on BC	Stockholm ca-co study	New Hampshire BC study	Italian ca-co study on BC	Brescia BC study	NESCC	South and East China ca-co study	Molecular epidemiology of BC	Italian ca-co study	Pooled estimate	Test for heterogeneity
Total vegetables													
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	0.95 (0.79–1.13)	0.76 (0.51–1.13)	0.86 (0.54–1.37)	1.12 (0.74–1.68)	1.00 (0.65–1.53)	0.74 (0.57–0.94)	1.05 (0.64–1.72)	1.00 (0.83–1.20)	0.65 (0.47–0.89)	1.30 (0.62–2.69)	0.79 (0.60–1.05)	0.91 (0.83–0.99)	I ² =0.0%, p=0.442
Q3	0.74 (0.62–0.88)	0.87 (0.58–1.30)	1.01 (0.63–1.62)	1.04 (0.70–1.56)	1.14 (0.74–1.76)	0.55 (0.43–0.71)	1.04 (0.64–1.71)	0.98 (0.82–1.18)	0.82 (0.59–1.13)	0.80 (0.38–1.66)	0.79 (0.60–1.05)	0.82 (0.70–0.94)	I ² =52.9%, p=0.020
Leaf vegetables													
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	0.82 (0.69–0.98)	0.68 (0.46–1.00)	0.70 (0.44–1.12)	0.82 (0.56–1.20)	0.94 (0.61–1.45)	0.65 (0.43–0.98)	0.59 (0.36–0.97)	1.16 (0.96–1.39)	1.36 (0.99–1.87)	0.77 (0.36–1.64)	0.81 (0.63–1.05)	0.84 (0.71–0.96)	I ² =50.7%, p=0.027
Q3	0.76 (0.63–0.91)	0.55 (0.36–0.83)	0.82 (0.51–1.32)	0.75 (0.48–1.17)	0.94 (0.62–1.44)	0.59 (0.47–0.74)	0.97 (0.57–1.66)	1.07 (0.89–1.29)	1.38 (1.00–1.91)	0.82 (0.40–1.69)	0.92 (0.67–1.26)	0.82 (0.68–0.96)	I ² =63.9%, p=0.002
Brassica													
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2			0.74 (0.47–1.17)		0.85 (0.54–1.36)								I ² =0.0%, p=0.687
Q3			0.82 (0.50–1.35)		1.53 (0.91–2.59)								I ² =55.0%, p=0.136
Stalk vegetables													
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	0.94 (0.19–4.61)	0.94 (0.19–4.61)	0.92 (0.58–1.47)	1.05 (0.72–1.52)	0.87 (0.57–1.33)	1.06 (0.67–1.68)	1.18 (0.73–1.90)	0.89 (0.67–1.19)	0.89 (0.67–1.19)	0.97 (0.71–1.33)	0.97 (0.71–1.33)	0.95 (0.80–1.09)	I ² =0.0%, p=0.977
Q3	0.39 (0.07–2.21)	0.39 (0.07–2.21)	0.97 (0.61–1.54)	1.06 (0.67–1.68)	1.17 (0.73–1.88)	1.06 (0.67–1.68)	0.77 (0.45–1.33)	1.34 (0.89–2.00)	1.34 (0.89–2.00)	0.66 (0.50–0.87)	0.66 (0.50–0.87)	0.87 (0.67–1.08)	I ² =33.5%, p=0.172
Shoot vegetables													
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	1.00 (0.84–1.18)	0.88 (0.60–1.29)	0.92 (0.58–1.46)	1.53 (1.02–2.28)	0.95 (0.64–1.40)	1.06 (0.67–1.68)	1.06 (0.63–1.76)	0.97 (0.82–1.15)	1.13 (0.85–1.50)	0.88 (0.66–1.15)	0.88 (0.66–1.15)	0.97 (0.88–1.06)	I ² =0.0%, p=0.658
Q3	0.85 (0.71–1.01)	0.87 (0.58–1.32)	0.88 (0.55–1.42)	1.16 (0.76–1.77)	1.16 (0.64–2.10)	1.16 (0.76–1.77)	0.95 (0.57–1.59)	0.86 (0.69–1.06)	0.92 (0.60–1.40)	0.85 (0.64–1.12)	0.85 (0.64–1.12)	0.87 (0.78–0.96)	I ² =0.0%, p=0.967
Tubers													
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	1.04 (0.88–1.24)	0.84 (0.56–1.25)	0.84 (0.56–1.25)	0.84 (0.56–1.25)	0.86 (0.56–1.34)	0.84 (0.56–1.25)	0.48 (0.12–1.87)	0.48 (0.12–1.87)	0.48 (0.12–1.87)	0.84 (0.22–3.22)	0.84 (0.22–3.22)	0.95 (0.81–1.08)	I ² =0.0%, p=0.534
Q3	0.90 (0.75–1.08)	1.22 (0.79–1.89)	1.22 (0.79–1.89)	0.86 (0.57–1.30)	0.94 (0.61–1.46)	0.86 (0.57–1.30)	0.84 (0.22–3.22)	0.84 (0.22–3.22)	0.84 (0.22–3.22)	0.84 (0.22–3.22)	0.84 (0.22–3.22)	0.92 (0.78–1.06)	I ² =0.0%, p=0.803

Adjusted for age at study entry (<45 years, 45–49 years, 50–54 years, 55–59 years, 60–64 years, 65–69 years, 70–74 years, >75 years), gender, smoking status (current smoker/former smoker/never smoker), and pack years (<9 years, 9–17 years, 18–30 years, 31–46 years, >47 years)

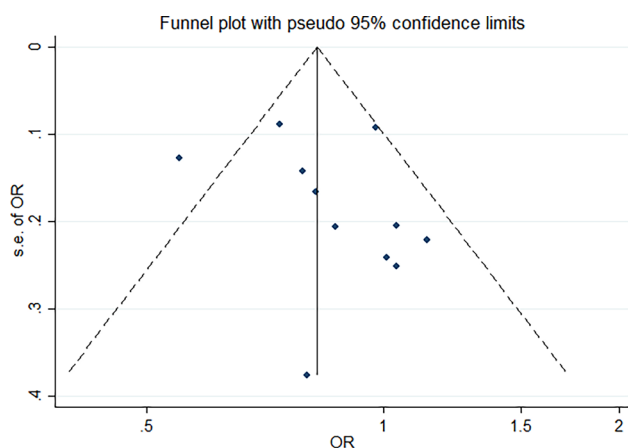


Fig. 3 Funnel plot of overall vegetable analyses results

studies [30, 31]. However, since some of our results have low heterogeneity, the role of bias is likely to have minimal influence on these results [32]. In addition, recall bias has been addressed and analyzed for its consequences in many epidemiological/methodological papers, and no clear answer on the magnitude of the effect of this specific type of bias could be drawn.

Several of our results revealed discrepancies among individual study findings and indicated significant heterogeneity in the effects of fruit and vegetable consumption on BC risk. This aligns with previous research highlighting the challenges of comparing diet-disease relationships globally due to variations in dietary habits and assessment methods across populations. For instance, differences in portion size estimations, nutrient databases used, and other factors contribute to result heterogeneity, complicating generalization and interpretation. Therefore, while our analysis focused on individual food items rather than overall dietary patterns, it is essential to consider the broader context of dietary diversity and assessment methods when interpreting these findings.

Strengths and limitations

This study has some limitations. First, the number of fruit and vegetable items described in each FFQ varied widely across the studies. Although it has been reported that fruit and vegetable servings increase with the number of fruit and

vegetable items on a questionnaire [33], the total of fruit and vegetable questions on the FFQs did not significantly modify the association between fruit or vegetable consumption and BC risk. In addition, the number of studies included in the fruit and vegetable subgroup analyses varied depending on whether the items comprising a particular fruit or vegetable subgroup were asked on the study-specific FFQs. Consequently, the power to examine associations for some subgroups is more limited compared with that for analyses of total fruit and total vegetables. Second, while case-control studies are valuable in investigating associations, they inherently possess limitations, particularly when assessing dietary factors which may be influenced by participants' cancer status [34]. Furthermore, as mentioned previously, case-control studies are generally considered to have higher risk of recall bias than cohort studies as the selection of the controls may be subject to population stratification [30]. We acknowledge that cohort studies and randomized controlled trials generally provide stronger evidence. Despite this, our analysis accounts for potential biases by addressing low heterogeneity across studies, suggesting minimal impact on our findings [32]. At last, while limited data on other potential BC risk factors such as body mass index and socioeconomic status were available, current literature suggests their contribution to BC risk is relatively small [35–38]. Besides, this pooled analysis also has several strengths, including the large sample size with harmonized variables across multiple studies, providing high statistical power to examine the role of total fruits and vegetables, subgroups of fruits and vegetables, and the possibility to perform subgroup analyses on gender and age. Moreover, we found low heterogeneity between studies for many of the association reported, the role of bias is likely to have minimal influence on our results.

Conclusion

This comprehensive study provides compelling evidence that the consumption of fruits overall, citrus fruits, pome fruits and tropical fruits reduce the BC risk. Besides, evidence was found for an inverse association between total vegetables and shoot vegetables intake.

Appendix 1: Food frequency questionnaires (Table 5)

Table 5 Detailed information on FFQs

Study name	Summary of dietary collection method	Food items asked (n)
The Los Angeles Bladder Cancer Study [39]	In-person interviews were conducted at subjects' homes, collecting information up to 2 years prior to cancer diagnosis for cases and index case diagnosis for controls. The structured questionnaire included forty food groups/items to assess dietary intake of vitamins A and C, carotenoids	49
South and East China case–control study on bladder and prostate cancer [12]	Trained interviewers, aware of the case–control status, used a food frequency questionnaire to collect data on the consumption of 35 specific food items within eight food groups, including dairy, eggs, fish, fruit, grain, meat, soy, and vegetables. Dietary information reflected the period of 1 year before the interview, with food intake categorized into six levels ranging from no intake to daily consumption	52
Belgian Case–Control study on Bladder Cancer [14]	The FFQ used was derived from the IMMIDIET study and comprised 788 food items, drawn from three existing food tables. Participants estimated their usual diet up to 12 months prior to the interview, reporting frequency and quantity of intake for each item	788
New Hampshire Bladder Cancer study [27]	A 121-item semi-quantitative FFQ, developed by Willett et al. for the Nurses' Health Study [REF], was used to assess participants' usual dietary intake. The questionnaire included food groups such as dairy, fruit, vegetables, eggs and meat, breads, beverages, and baked goods	121
Italian Case–Control study on Bladder Cancer [40]	Trained interviewers used a comprehensive standardized questionnaire to gather information from case patients and control subjects, covering sociodemographic details, lifestyle habits, medical history, occupational exposure, and chemical exposure. Interviews were conducted within a year of hospital admission	21
Molecular Epidemiology of Bladder Cancer and Prostate Cancer [9]	Participants were interviewed by a nurse using a standardized questionnaire to collect dietary data, including demographic information and personal habits such as smoking and alcohol consumption	90
The national enhanced cancer surveillance system [41]	A 70-item food frequency questionnaire, along with supplementary dietary habits, was utilized to gather data on the consumption of essential food items and nutrients, spanning two and 20 years before the interview. Questionnaires were dispatched to the patients within 1–4 months of diagnosis, and at requirement for controls	69
Brescia Bladder Cancer Case–control Study [17]	The dietary data collection process involved face-to-face interviews conducted during hospitalization by three experienced interviewers. A comprehensive semistructured questionnaire covered demographic, dietary, environmental, and occupational factors. It included sections on sociodemographic status, clinical data, dietary habits, tobacco and alcohol consumption, fluid intake, environmental exposure, and occupational history	40
Roswell Park Cancer Institute [18]	A 44-item food frequency questionnaire designed to assess dietary habits several years before diagnosis, focusing on intake of fruits, vegetables, cruciferous vegetables, and foods rich in vitamins A, C, and E, fat, and fiber was used	44
Stockholm case–control study [42]	Diet was assessed by an extensive semiquantitative food-frequency questionnaire including 188 food items (27 fried meat dishes, 16 roasted meat dishes, 11 boiled meat dishes, four grilled meat dishes, four gravies and sauces, seven fish dishes, fried eggs, omelettes, and black pudding). All questions referred to eating habits 5 years previously	188
Italian case–control study [43]	Trained personnel administered a standard, structured questionnaire to study subjects. Patients' dietary habits in the 2 years preceding study enrolment were collected through a validated and reproducible FFQ	77

FFQ food frequency questionnaire, BC bladder cancer

Appendix 2: Gender stratified results (Tables 6, 7, 8, 9)

Table 6 Odds ratios of bladder cancer by total fruit intake among men

	Los Angeles BC ca-co study	Roswell Park Cancer Institute	Belgian ca-co study on BC	Stockholm ca-co study	New Hampshire BC study	Italian ca-co study on BC	Brescia BC study	NESCC	South and East China ca-co study	Molecular epidemiology of BC	Italian ca-co study	Pooled estimate	Test for heterogeneity
Total fruits													
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	1.04 (0.86–1.27)	0.86 (0.55–1.35)	0.81 (0.48–1.36)	0.81 (0.51–1.31)	1.08 (0.63–1.84)	1.26 (1.00–1.60)	0.84 (0.50–1.41)	0.81 (0.64–1.01)	0.78 (0.55–1.10)	0.69 (0.32–1.51)	1.19 (0.87–1.62)	0.92 (0.81–1.02)	I ² =18.8%, p=0.264
Q3	0.94 (0.76–1.15)	0.80 (0.49–1.31)	0.47 (0.27–0.83)	0.88 (0.52–1.46)	1.02 (0.60–1.74)	0.93 (0.51–1.69)	1.41 (0.85–2.35)	0.93 (0.74–1.17)	0.71 (0.49–1.02)	0.71 (0.31–1.63)	0.88 (0.64–1.19)	0.83 (0.71–0.95)	I ² =25.7%, p=0.199
Citrus fruits													
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	1.05 (0.86–1.28)	0.61 (0.40–0.93)	1.05 (0.63–1.77)	1.14 (0.74–1.77)	0.96 (0.56–1.65)	1.14 (0.74–1.77)	0.81 (0.49–1.34)	0.94 (0.76–1.17)	0.79 (0.52–1.19)	0.69 (0.29–1.65)	0.95 (0.73–1.26)	0.86 (0.73–1.00)	I ² =40.9%, p=0.085
Q3	0.93 (0.75–1.14)	0.76 (0.45–1.30)	0.79 (0.46–1.37)	0.68 (0.37–1.26)	0.87 (0.51–1.48)	0.68 (0.37–1.26)	1.06 (0.64–1.77)	1.07 (0.82–1.39)	0.65 (0.45–0.93)	0.49 (0.18–1.32)	1.57 (1.07–2.32)	0.87 (0.72–1.01)	I ² =32.5%, p=0.148
Pome fruits													
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	0.98 (0.65–1.49)	0.77 (0.41–1.45)	0.87 (0.55–1.40)	0.79 (0.47–1.34)	1.34 (0.69–2.60)	1.34 (0.69–2.60)	1.41 (0.90–2.23)	0.97 (0.78–1.21)	0.76 (0.55–1.04)	0.45 (0.18–1.12)	1.00 (0.75–1.34)	0.94 (0.78–1.11)	I ² =22.5%, p=0.258
Q3	0.77 (0.41–1.45)	0.77 (0.41–1.45)	0.79 (0.47–1.34)	0.79 (0.47–1.34)	1.22 (0.74–2.02)	1.22 (0.74–2.02)	0.74 (0.32–1.70)	0.83 (0.65–1.07)	0.76 (0.48–1.20)	0.36 (0.15–0.85)	0.94 (0.67–1.31)	0.77 (0.58–0.97)	I ² =40.2%, p=0.123
Tropical fruits													
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	1.16 (0.95–1.41)	0.82 (0.53–1.28)	0.86 (0.53–1.39)	0.86 (0.53–1.39)	1.00 (0.58–1.71)	1.00 (0.58–1.71)	1.30 (0.77–2.19)	1.02 (0.82–1.27)	0.76 (0.55–1.04)	1.67 (0.57–4.92)	1.19 (0.87–1.61)	0.99 (0.88–1.11)	I ² =6.1%, P=0.384
Q3	0.97 (0.79–1.19)	0.86 (0.52–1.42)	0.85 (0.52–1.40)	0.85 (0.52–1.40)	1.30 (0.76–2.22)	1.30 (0.76–2.22)	0.99 (0.61–1.62)	0.88 (0.69–1.12)	0.76 (0.48–1.20)	1.54 (0.61–3.87)	0.78 (0.57–1.07)	0.89 (0.79–1.00)	I ² =0.0%, p=0.863

Adjusted for age at study entry (<45 years, 45–49 years, 50–54 years, 55–59 years, 60–64 years, 65–69 years, 70–74 years, >75 years), smoking status (current smoker/former smoker/never smoker), and pack years (<9 years, 9–17 years, 18–30 years, 31–46 years, >47 years)

Table 7 Odds ratios of bladder cancer by total fruit intake among women

	Los Angeles BC ca-co study	Roswell Park Cancer Institute	Belgian ca-co study on BC	Stockholm ca-co study	New Hampshire BC study	Italian ca-co study on BC	NESCC	South and East China ca-co study	Molecular epidemiology of BC	Italian ca-co study	Pooled estimate	Test for heterogeneity
Total fruits												
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	0.68 (0.44–1.04)	0.53 (0.22–1.27)	0.68 (0.24–1.97)	1.07 (0.50–2.28)	1.24 (0.58–2.65)	0.81 (0.50–1.31)	0.81 (0.60–1.10)	0.78 (0.36–1.70)	5.68 (0.43–74.39)	0.88 (0.41–1.86)	0.76 (0.61–0.90)	$I^2=0.0\%$, $p=0.781$
Q3	0.65 (0.43–0.97)	0.66 (0.29–1.50)	0.60 (0.21–1.67)	1.00 (0.47–2.12)	0.91 (0.42–1.99)	0.70 (0.24–2.09)	0.70 (0.51–0.96)	0.25 (0.12–0.53)	2.23 (0.29–17.20)	1.28 (0.59–2.78)	0.60 (0.40–0.80)	$I^2=43.3\%$, $p=0.070$
Citrus fruits												
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	0.69 (0.46–1.05)	0.51 (0.23–1.13)	0.95 (0.33–2.71)	0.77 (0.38–1.58)	0.96 (0.45–2.05)	1.02 (0.77–1.35)	1.02 (0.77–1.35)	0.79 (0.34–1.84)	0.04 (0.00–2.51)	1.14 (0.60–2.17)	0.78 (0.61–0.95)	$I^2=6.6\%$, $p=0.380$
Q3	0.62 (0.42–0.92)	0.39 (0.17–0.92)	0.52 (0.19–1.45)	0.82 (0.38–1.80)	1.26 (0.57–2.75)	0.99 (0.70–1.41)	0.99 (0.70–1.41)	0.26 (0.13–0.51)	0.03 (0.00–1.45)	1.47 (0.56–3.85)	0.56 (0.32–0.80)	$I^2=62.5\%$, $p=0.006$
Pome fruits												
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	0.76 (0.37–1.59)	0.76 (0.37–1.59)	0.76 (0.37–1.59)	0.74 (0.35–1.57)	1.37 (0.53–3.59)	0.82 (0.61–1.09)	0.82 (0.61–1.09)	0.62 (0.30–1.29)	2.33 (0.25–21.73)	0.62 (0.30–1.29)	0.78 (0.59–0.97)	$I^2=0.0\%$, $p=0.953$
Q3	0.45 (0.16–1.24)	0.45 (0.16–1.24)	0.45 (0.16–1.24)	1.21 (0.59–2.49)	0.68 (0.34–1.36)	0.66 (0.47–0.92)	0.66 (0.47–0.92)	0.33 (0.15–0.74)	1.81 (0.22–14.98)	0.33 (0.15–0.74)	0.58 (0.42–0.73)	$I^2=0.0\%$, $p=0.476$
Tropical fruits												
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	1.18 (0.76–1.81)	1.58 (0.71–3.52)	1.58 (0.71–3.52)	1.44 (0.68–3.07)	0.64 (0.29–1.38)	0.86 (0.64–1.15)	0.86 (0.64–1.15)	0.52 (0.25–1.06)	2.85 (0.20–40.70)	0.94 (0.43–2.05)	0.82 (0.63–1.01)	$I^2=6.2\%$, $p=0.383$
Q3	0.99 (0.66–1.48)	1.10 (0.44–2.75)	1.10 (0.44–2.75)	1.21 (0.57–2.57)	0.67 (0.31–1.44)	0.70 (0.51–0.95)	0.70 (0.51–0.95)	0.19 (0.08–0.47)	1.04 (0.12–9.21)	0.83 (0.39–1.78)	0.69 (0.39–1.00)	$I^2=69.6\%$, $p=0.002$

Adjusted for age at study entry (<45 years, 45–49 years, 50–54 years, 55–59 years, 60–64 years, 65–69 years, 70–74 years, >75 years), smoking status (current smoker/former smoker/never smoker), and pack years (<9 years, 9–17 years, 18–30 years, 31–46 years, >47 years)

Table 8 Odds ratios of bladder cancer by total vegetable intake stratified by men

	Los Angeles BC ca-co study	Roswell Park Cancer Institute	Belgian ca-co study on BC	Stockholm ca-co study	New Hampshire BC study	Italian ca-co study on BC	Brescia BC study	NESCC	South and East China ca-co study	Molecular epidemiology of BC	Italian ca-co study	Pooled estimate	Test for heterogeneity
Total vegetables													
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	0.90 (0.74–1.11)	0.92 (0.58–1.45)	0.72 (0.43–1.22)	1.25 (0.76–2.05)	0.85 (0.50–1.44)	0.72 (0.55–0.95)	1.01 (0.61–1.68)	0.99 (0.79–1.25)	0.56 (0.40–0.81)	0.86 (0.39–1.92)	0.68 (0.50–0.93)	0.80 (0.70–0.91)	I ² =26.8%, p=0.189
Q3	0.71 (0.58–0.86)	1.29 (0.80–2.06)	0.93 (0.55–1.60)	0.90 (0.55–1.45)	0.94 (0.55–1.62)	0.69 (0.52–0.91)	1.11 (0.67–1.86)	0.97 (0.77–1.22)	0.91 (0.63–1.32)	0.62 (0.28–1.41)	0.77 (0.56–1.04)	0.80 (0.71–0.88)	I ² =1.0%, p=0.432
Leaf vegetables													
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	0.80 (0.66–0.97)	0.81 (0.52–1.26)	0.65 (0.39–1.11)	0.80 (0.50–1.26)	1.23 (0.72–2.10)	0.57 (0.36–0.90)	0.59 (0.36–0.97)	1.27 (1.00–1.60)	1.62 (1.13–2.32)	0.72 (0.32–1.65)	0.77 (0.59–1.02)	0.84 (0.68–0.99)	I ² =57.5%, p=0.009
Q3	0.76 (0.62–0.93)	0.70 (0.44–1.13)	0.62 (0.36–1.07)	0.70 (0.41–1.19)	0.86 (0.51–1.45)	0.71 (0.55–0.92)	0.97 (0.57–1.66)	1.14 (0.90–1.45)	1.72 (1.19–2.48)	0.61 (0.28–1.35)	1.03 (0.72–1.45)	0.84 (0.70–0.98)	I ² =46.1%, p=0.046
Shoot vegetables													
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	1.09 (0.90–1.33)	1.13 (0.72–1.75)	0.89 (0.53–1.49)	1.53 (0.93–2.53)	1.14 (0.70–1.85)		1.06 (0.63–1.76)	0.90 (0.73–1.11)	1.26 (0.92–1.73)		0.79 (0.59–1.07)	0.99 (0.88–1.11)	I ² =6.8%, p=0.378
Q3	0.85 (0.70–1.05)	1.24 (0.76–2.01)	0.76 (0.44–1.32)	1.08 (0.65–1.81)	1.49 (0.71–3.15)		0.95 (0.57–1.59)	0.84 (0.64–1.11)	1.34 (0.82–2.17)		0.84 (0.62–1.15)	0.89 (0.78–1.00)	I ² =0.0%, p=0.751

Adjusted for age at study entry (<45 years, 45–49 years, 50–54 years, 55–59 years, 60–64 years, 65–69 years, 70–74 years, >75 years), smoking status (current smoker/former smoker/never smoker), and pack years (<9 years, 9–17 years, 18–30 years, 31–46 years, >47 years)

Table 9 Odds ratios of bladder cancer by total vegetable intake stratified by women

	Los Angeles BC ca-co study	Roswell Park Cancer Institute	Belgian ca-co study on BC	Stockholm ca-co study	New Hampshire BC study	Italian ca-co study on BC	NESCC	South and East China ca-co study	Molecular epidemiology of BC	Italian ca-co study	Pooled estimate	Test for heterogeneity
Total vegetables												
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	1.21 (0.82–1.79)	0.40 (0.17–0.93)	0.82 (0.28–2.39)	0.90 (0.43–1.91)	1.41 (0.65–3.10)	0.62 (0.35–1.10)	1.05 (0.77–1.43)	1.16 (0.54–2.52)	2.97 (0.38–23.27)	1.01 (0.45–2.23)	0.86 (0.64–1.08)	$I^2 = 24.1\%$ $p = 0.222$
Q3	0.89 (0.59–1.33)	0.38 (0.18–0.84)	0.87 (0.32–2.39)	1.24 (0.59–2.64)	1.59 (0.74–3.44)	0.18 (0.09–0.34)	0.98 (0.72–1.34)	0.65 (0.33–1.31)	2.50 (0.32–19.57)	0.67 (0.32–1.44)	0.71 (0.39–1.02)	$I^2 = 78.2\%$ $p = 0.000$
Leaf vegetables												
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	1.01 (0.68–1.49)	0.42 (0.19–0.94)	0.64 (0.20–2.04)	0.86 (0.43–1.72)	0.53 (0.24–1.18)	0.85 (0.35–2.08)	1.00 (0.73–1.37)	0.69 (0.35–1.36)	1.60 (0.21–12.15)	0.85 (0.42–1.73)	0.77 (0.61–0.94)	$I^2 = 0.0\%$ $p = 0.534$
Q3	0.77 (0.52–1.15)	0.26 (0.11–0.60)	1.78 (0.62–5.09)	0.96 (0.42–2.20)	1.03 (0.49–2.17)	0.26 (0.15–0.46)	0.95 (0.70–1.28)	0.61 (0.30–1.25)	2.09 (0.31–14.30)	0.51 (0.23–1.10)	0.61 (0.37–0.85)	$I^2 = 68.8\%$ $p = 0.001$
Shoot vegetables												
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	0.71 (0.48–1.04)	0.46 (0.20–1.05)	1.11 (0.35–3.51)	1.48 (0.73–2.98)	0.63 (0.31–1.27)	1.12 (0.85–1.47)	1.12 (0.85–1.47)	0.70 (0.37–1.31)	1.06 (0.50–2.23)	1.06 (0.50–2.23)	0.80 (0.60–1.00)	$I^2 = 25.7\%$ $p = 0.224$
Q3	0.83 (0.56–1.24)	0.34 (0.15–0.76)	1.46 (0.52–4.14)	1.34 (0.63–2.83)	0.68 (0.25–1.89)	0.89 (0.62–1.28)	0.89 (0.62–1.28)	0.26 (0.10–0.65)	0.76 (0.36–1.60)	0.76 (0.36–1.60)	0.65 (0.39–0.90)	$I^2 = 57.2\%$ $p = 0.022$

Adjusted for age at study entry (< 45 years, 45–49 years, 50–54 years, 55–59 years, 60–64 years, 65–69 years, 70–74 years, > 75 years), smoking status (current smoker/former smoker/never smoker), and pack years (< 9 years, 9–17 years, 18–30 years, 31–46 years, > 47 years)

Appendix 3: Age stratified results (Tables 10, 11, 12, 13)

Table 10 Odds ratios of bladder cancer by total fruit intake stratified by age <60 years old

	Los Angeles BC ca-co study	Roswell Park Cancer Institute	Belgian ca-co study on BC	Stockholm ca-co study	New Hampshire BC study	Italian ca-co study on BC	Brescia BC study	NESCC	South and East China ca-co study	Molecular epidemiology of BC	Italian ca-co study	Pooled estimate	Test for heterogeneity
Total fruits	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q1	0.95 (0.77–1.17)	0.75 (0.38–1.47)	0.55 (0.23–1.32)	0.85 (0.27–2.71)	1.35 (0.68–2.68)	0.98 (0.69–1.39)	0.86 (0.35–2.12)	0.83 (0.60–1.13)	0.67 (0.39–1.17)	1.12 (0.48–2.63)	1.45 (0.81–2.62)	0.88 (0.76–1.01)	I ² =0.0%, p=0.796
Q2	0.79 (0.63–0.98)	0.80 (0.39–1.63)	0.44 (0.16–1.18)	1.20 (0.38–3.78)	1.13 (0.52–2.44)	0.83 (0.35–1.96)	1.45 (0.57–3.67)	0.75 (0.53–1.05)	0.58 (0.34–0.99)	0.81 (0.33–1.99)	1.14 (0.63–2.06)	0.76 (0.64–0.88)	I ² =0.0%, p=0.855
Citrus fruits	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q1	0.95 (0.77–1.18)	0.40 (0.21–0.77)	0.84 (0.35–1.98)	0.76 (0.28–2.08)	1.30 (0.63–2.67)	0.84 (0.34–2.11)	1.12 (0.84–1.50)	1.12 (0.84–1.50)	0.93 (0.49–1.77)	0.36 (0.13–0.99)	1.27 (0.74–2.17)	0.82 (0.59–1.06)	I ² =55.3%, p=0.017
Q2	0.73 (0.59–0.92)	0.70 (0.32–1.53)	0.86 (0.33–2.24)	1.06 (0.22–5.21)	1.26 (0.58–2.72)	1.09 (0.44–2.70)	1.20 (0.81–1.78)	1.20 (0.81–1.78)	0.56 (0.33–0.93)	0.65 (0.21–2.06)	1.13 (0.56–2.28)	0.77 (0.64–0.91)	I ² =0.0%, p=0.743
Pome fruits	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q1	0.71 (0.39–1.31)	0.34 (0.11–1.07)	0.57 (0.17–1.87)	1.36 (0.40–4.58)	1.62 (0.63–4.15)	1.09 (0.44–2.70)	0.69 (0.50–0.95)	0.69 (0.50–0.95)	0.57 (0.30–1.09)	0.49 (0.18–1.32)	1.20 (0.69–2.09)	0.71 (0.53–0.89)	I ² =0.0%, p=0.600
Q2	0.34 (0.11–1.07)	0.34 (0.11–1.07)	0.57 (0.17–1.87)	1.36 (0.40–4.58)	1.62 (0.63–4.15)	1.09 (0.44–2.70)	0.69 (0.50–0.95)	0.69 (0.50–0.95)	0.57 (0.30–1.09)	0.49 (0.18–1.32)	1.20 (0.69–2.09)	0.71 (0.53–0.89)	I ² =15.3%, p=0.315
Tropical fruits	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q1	1.03 (0.83–1.27)	1.11 (0.59–2.06)	1.37 (0.42–4.41)	1.37 (0.42–4.41)	0.94 (0.45–1.96)	0.94 (0.45–1.96)	0.63 (0.24–1.67)	0.92 (0.68–1.25)	0.74 (0.45–1.21)	1.04 (0.32–3.46)	1.24 (0.68–2.29)	0.95 (0.81–1.10)	I ² =0.0%, p=0.911
Q2	0.94 (0.76–1.17)	0.65 (0.27–1.53)	1.19 (0.37–3.84)	1.19 (0.37–3.84)	1.28 (0.61–2.72)	1.28 (0.61–2.72)	1.29 (0.53–3.13)	0.84 (0.59–1.20)	0.57 (0.30–1.09)	1.05 (0.38–1.09)	0.66 (0.36–1.21)	0.84 (0.70–0.98)	I ² =0.0%, p=0.703

Adjusted for age at study entry (<45 years, 45–49 years, 50–54 years, 55–59 years), gender, smoking status (current smoker/former smoker/never smoker), and pack years (<9 years, 9–17 years, 18–30 years, 31–46 years, >47 years)

Table 11 Odds ratios of bladder cancer by total fruit intake stratified by age ≥ 60 years old

	Los Angeles BC ca-co study	Roswell Park Cancer Institute	Belgian ca-co study on BC	Stockholm ca-co study	New Hampshire BC study	Italian ca-co study on BC	Brescia BC study	NESCC	South and East China ca-co study	Molecular epidemiology of BC	Italian ca-co study	Pooled estimate	Test for heterogeneity
Total fruits													
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	0.95 (0.68–1.32)	0.76 (0.47–1.25)	0.87 (0.50–1.49)	0.90 (0.59–1.38)	0.94 (0.53–1.68)	1.24 (0.95–1.62)	0.86 (0.46–1.60)	0.85 (0.68–1.06)	0.86 (0.58–1.27)	0.36 (0.08–1.58)	1.07 (0.77–1.48)	0.91 (0.81–1.02)	I ² =0.0%, p=0.647
Q3	0.93 (0.67–1.28)	0.71 (0.42–1.17)	0.51 (0.29–0.90)	0.84 (0.53–1.31)	0.88 (0.51–1.52)	0.90 (0.47–1.74)	1.40 (0.76–2.58)	0.91 (0.73–1.14)	0.55 (0.37–0.83)	0.66 (0.20–2.18)	0.89 (0.64–1.24)	0.80 (0.69–0.91)	I ² =5.5%, p=0.391
Citrus fruits													
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	0.99 (0.71–1.37)	0.74 (0.47–1.16)	1.09 (0.63–1.88)	1.08 (0.72–1.61)	0.74 (0.42–1.29)	0.80 (0.44–1.46)	0.80 (0.44–1.46)	0.92 (0.75–1.13)	0.71 (0.45–1.11)	0.69 (0.19–2.43)	0.93 (0.70–1.23)	0.88 (0.78–0.99)	I ² =0.0%, p=0.898
Q3	1.03 (0.75–1.42)	0.60 (0.34–1.03)	0.64 (0.37–1.10)	0.77 (0.46–1.26)	0.81 (0.47–1.40)	1.06 (0.57–1.96)	1.06 (0.57–1.96)	0.99 (0.78–1.27)	0.51 (0.34–0.78)	0.09 (0.01–0.85)	1.74 (1.14–2.66)	0.80 (0.62–0.99)	I ² =53.2%, p=0.023
Pome fruits													
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	1.04 (0.67–1.62)	0.85 (0.47–1.54)	0.85 (0.55–1.29)	0.85 (0.55–1.29)	1.20 (0.61–2.38)	1.53 (0.89–2.64)	1.53 (0.89–2.64)	1.04 (0.84–1.28)	0.70 (0.49–1.00)	0.66 (0.17–2.51)	0.90 (0.66–1.23)	0.99 (0.84–1.13)	I ² =0.0%, p=0.789
Q3	0.85 (0.47–1.54)	0.85 (0.47–1.54)	0.87 (0.55–1.36)	0.87 (0.55–1.36)	0.83 (0.50–1.37)	0.92 (0.38–2.25)	0.92 (0.38–2.25)	0.90 (0.71–1.14)	0.54 (0.33–0.91)	0.60 (0.17–2.16)	0.78 (0.56–1.10)	0.85 (0.71–0.99)	I ² =0.0%, p=0.996
Tropical fruits													
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	1.40 (1.00–1.94)	0.89 (0.55–1.44)	0.99 (0.64–1.53)	0.99 (0.64–1.53)	0.82 (0.47–1.44)	1.71 (0.91–3.22)	1.71 (0.91–3.22)	1.00 (0.80–1.23)	0.70 (0.49–1.00)	2.76 (0.74–10.23)	1.11 (0.80–1.53)	0.97 (0.82–1.13)	I ² =24.2%, p=0.228
Q3	0.94 (0.68–1.28)	0.91 (0.55–1.52)	0.90 (0.58–1.38)	0.90 (0.58–1.38)	0.98 (0.57–1.69)	0.84 (0.46–1.51)	0.84 (0.46–1.51)	0.84 (0.67–1.05)	0.54 (0.33–0.91)	1.24 (0.33–4.68)	0.84 (0.60–1.15)	0.83 (0.72–0.95)	I ² =0.0%, p=0.781

Adjusted for age at study entry (60–64 years, 65–69 years, 70–74 years, > 75 years), gender, smoking status (current smoker/former smoker/never smoker), and pack years (< 9 years, 9–17 years, 18–30 years, 31–46 years, > 47 years)

Table 12 Odds ratios of bladder cancer by total vegetable intake stratified by age < 60 years old

	Los Angeles BC ca-co study	Roswell Park Cancer Institute	Belgian ca-co study on BC	Stockholm ca-co study	New Hampshire BC study	Italian ca-co study on BC	Brescia BC study	NESCC	South and East China ca-co study	Molecular epidemiology of BC	Italian ca-co study	Pooled estimate	Test for heterogeneity
Total vegetables													
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	0.97 (0.78–1.20)	0.70 (0.37–1.34)	0.61 (0.23–1.64)	1.51 (0.45–5.15)	0.82 (0.40–1.70)	0.50 (0.33–0.77)	0.85 (0.35–2.07)	1.08 (0.79–1.48)	0.62 (0.36–1.09)	1.09 (0.43–2.76)	1.08 (0.59–1.99)	0.80 (0.63–0.97)	I ² = 30.8%, p = 0.153
Q3	0.78 (0.62–0.97)	0.97 (0.47–2.02)	0.75 (0.30–1.83)	1.51 (0.47–4.87)	2.19 (1.02–4.69)	0.37 (0.24–0.57)	0.59 (0.22–1.56)	0.83 (0.59–1.18)	0.82 (0.47–1.43)	0.63 (0.26–1.54)	0.71 (0.39–1.29)	0.70 (0.52–0.88)	I ² = 47.8%, p = 0.038
Leaf vegetables													
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	0.86 (0.70–1.07)	0.88 (0.47–1.64)	0.77 (0.30–1.98)	1.06 (0.34–3.24)	1.57 (0.74–3.32)	0.48 (0.24–0.96)	0.60 (0.24–1.50)	1.14 (0.82–1.58)	1.43 (0.83–2.45)	0.70 (0.27–1.80)	0.55 (0.32–0.96)	0.80 (0.64–0.97)	I ² = 24.0%, p = 0.215
Q3	0.70 (0.56–0.87)	0.55 (0.26–1.17)	0.76 (0.30–1.91)	0.56 (0.15–2.12)	2.37 (1.09–5.14)	0.51 (0.34–0.74)	1.55 (0.60–4.02)	0.89 (0.63–1.25)	1.32 (0.77–2.25)	0.55 (0.22–1.39)	0.98 (0.51–1.87)	0.70 (0.56–0.84)	I ² = 20.0%, p = 0.253
Shoot vegetables													
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	1.06 (0.86–1.31)	0.99 (0.52–1.92)	0.68 (0.25–1.83)	2.30 (0.72–7.34)	1.16 (0.60–2.23)		1.13 (0.43–2.97)	1.13 (0.83–1.52)	1.01 (0.63–1.62)		1.09 (0.61–1.93)	1.06 (0.90–1.22)	I ² = 0.0%, p = 0.988
Q3	0.88 (0.70–1.09)	1.09 (0.53–2.26)	0.57 (0.22–1.51)	1.03 (0.31–3.36)	1.63 (0.55–4.86)		0.52 (0.21–1.30)	0.85 (0.55–1.32)	0.87 (0.43–1.75)		0.70 (0.38–1.29)	0.83 (0.68–0.97)	I ² = 0.0%, p = 0.910

Adjusted for age at study entry (< 45 years, 45–49 years, 50–54 years, 55–59 years), gender, smoking status (current smoker/former smoker/never smoker), and pack years (< 9 years, 9–17 years, 18–30 years, 31–46 years, > 47 years)

Table 13 Odds ratios of bladder cancer by total vegetable intake stratified by age ≥ 60 years old

	Los Angeles BC ca-co study	Roswell Park Cancer Institute	Belgian ca-co study on BC	Stockholm ca-co study	New Hampshire BC study	Italian ca-co study on BC	Brescia BC study	NESCC	South and East China ca-co study	Molecular epidemiology of BC	Italian ca-co study	Pooled estimate	Test for heterogeneity
Total vegetables													
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	0.87 (0.61–1.24)	0.79 (0.48–1.31)	0.85 (0.50–1.46)	1.04 (0.67–1.62)	1.06 (0.61–1.85)	0.84 (0.62–1.15)	1.14 (0.61–2.12)	0.95 (0.76–1.19)	0.68 (0.46–1.02)	0.84 (0.22–3.21)	0.65 (0.47–0.89)	0.82 (0.72–0.92)	I ² = 0.0%, p = 0.714
Q3	0.64 (0.45–0.90)	0.91 (0.56–1.48)	0.98 (0.56–1.72)	0.94 (0.61–1.45)	0.80 (0.47–1.39)	0.68 (0.50–0.93)	1.44 (0.77–2.68)	1.01 (0.81–1.25)	0.89 (0.59–1.33)	1.17 (0.32–4.29)	0.77 (0.55–1.06)	0.81 (0.71–0.91)	I ² = 0.0%, p = 0.481
Leaf vegetables													
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	0.75 (0.54–1.04)	0.60 (0.37–0.98)	0.66 (0.38–1.13)	0.76 (0.50–1.14)	0.74 (0.43–1.28)	0.76 (0.45–1.29)	0.56 (0.31–1.02)	1.16 (0.92–1.46)	1.40 (0.94–2.09)	1.06 (0.27–4.17)	0.88 (0.65–1.18)	0.81 (0.67–0.95)	I ² = 36.7%, p = 0.106
Q3	0.96 (0.68–1.37)	0.54 (0.33–0.88)	0.87 (0.49–1.53)	0.76 (0.47–1.23)	0.62 (0.36–1.05)	0.66 (0.49–0.88)	0.77 (0.40–1.49)	1.14 (0.91–1.43)	1.63 (1.06–2.50)	1.25 (0.35–4.41)	0.88 (0.62–1.27)	0.83 (0.67–0.99)	I ² = 49.3%, p = 0.032
Shoot vegetables													
Q1	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Q2	0.93 (0.66–1.29)	0.86 (0.53–1.38)	1.01 (0.59–1.72)	1.46 (0.95–2.25)	0.85 (0.52–1.40)		1.08 (0.58–2.00)	0.92 (0.75–1.13)	1.29 (0.90–1.86)		0.76 (0.55–1.05)	0.92 (0.81–1.04)	I ² = 0.0%, p = 0.538
Q3	0.80 (0.57–1.13)	0.77 (0.46–1.28)	1.01 (0.57–1.79)	1.19 (0.75–1.88)	0.98 (0.48–2.02)		1.27 (0.68–2.37)	0.87 (0.67–1.12)	1.04 (0.60–1.78)		0.87 (0.63–1.21)	0.89 (0.76–1.01)	I ² = 0.0%, p = 0.932

Adjusted for age at study entry (60–64 years, 65–69 years, 70–74 years, > 75 years), gender, smoking status (current smoker/former smoker/never smoker), and pack years (< 9 years, 9–17 years, 18–30 years, 31–46 years, > 47 years)

Acknowledgements We gratefully acknowledge all principal investigators for their willingness to participate in this joint project.

Funding The Stockholm Case–control study was supported by grant from the Swedish National Cancer Society and from the Swedish Work Environment Fund. The Roswell Park Memorial Institute Case–control study on bladder cancer was supported by Public Health Service Grants CA11535 and CA16056 from the National Cancer Institute. The Italian Case–control study on bladder cancer was conducted within the framework of the CNR (Italian National Research Council) Applied Project “Clinical Application of Oncological Research” (contracts 94.01321.PF39 and 94.01119.PF39), and with the contributions of the Italian Association for Cancer Research, the Italian League against Tumours, Milan, and Mrs. Angela Marchegiano Borgomainerio. The Brescia bladder cancer study was partly supported by the International Agency for Research on Cancer. The Molecular Epidemiology of Bladder Cancer and Prostate Cancer was supported in part by grants ES06718 (to Z.-F.Z.), U01 CA96116 (to A.B.), and CA09142 from the NIH National Institute of Environmental Health Sciences, the National Cancer Institute, the Department of Health and Human Services, and by the Ann Fitzpatrick Alper Program in Environmental Genomics at the Jonsson Comprehensive Cancer Center, UCLA.

Data availability The data that support the findings of this study are available on request from the corresponding author.

Declarations

Conflict of interest All the authors declare no conflict of interest.

Ethical approval protocol numbers The Los Angeles Bladder cancer study: HS-05-00222; South and East China case–control study: not yet available; Belgian case–control study: not yet available; New Hampshire bladder cancer study: not yet available; Italian case–control study on bladder cancer: INT32/09; Molecular epidemiology of bladder cancer study: IRB#11-001325; NECSS: not yet available; Brescia bladder cancer study: 2859/9185; Roswell park cancer institute: EDR 122807; Stockholm case–control study: not yet available; Italian case–control study: not yet available.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.



References

- Liu RH (2013) Dietary bioactive compounds and their health implications. *J Food Sci* 78(Suppl 1):A18–25. <https://doi.org/10.1111/1750-3841.12101>
- Clinton SK, Giovannucci EL, Hursting SD (2020) The World Cancer Research Fund/American Institute for Cancer Research third expert report on diet, nutrition, physical activity, and cancer: impact and future directions. *J Nutr* 150(4):663–671. <https://doi.org/10.1093/jn/nxz268>
- Al-Zalabani AH, Stewart KF, Wesselius A, Schols AM, Zeegers MP (2016) Modifiable risk factors for the prevention of bladder cancer: a systematic review of meta-analyses. *Eur J Epidemiol* 31(9):811–851. <https://doi.org/10.1007/s10654-016-0138-6>
- Fankhauser CD, Mostafid H (2018) Prevention of bladder cancer incidence and recurrence: nutrition and lifestyle. *Curr Opin Urol* 28(1):88–92. <https://doi.org/10.1097/mou.0000000000000452>
- Panche AN, Diwan AD, Chandra SR (2016) Flavonoids: an overview. *J Nutr Sci* 5:e47. <https://doi.org/10.1017/jns.2016.41>
- Goossens ME, Isa F, Brinkman M, Mak D, Reulen R, Wesselius A, Benhamou S, Bosetti C, Bueno-de-Mesquita B, Carta A, Allam MF, Golka K, Grant EJ, Jiang X, Johnson KC, Karagas MR, Kellen E, La Vecchia C, Lu CM, Marshall J, Moysich K, Pohlabein H, Porru S, Steineck G, Stern MC, Tang L, Taylor JA, van den Brandt P, Villeneuve PJ, Wakai K, Weiderpass E, White E, Wolk A, Zhang ZF, Buntinx F, Zeegers MP (2016) International pooled study on diet and bladder cancer: the bladder cancer, epidemiology and nutritional determinants (BLEND) study: design and baseline characteristics. *Arch Public Health* 74:30. <https://doi.org/10.1186/s13690-016-0140-1>
- Smith-Warner SA, Spiegelman D, Ritz J, Albanes D, Beeson WL, Bernstein L, Berrino F, van den Brandt PA, Buring JE, Cho E, Colditz GA, Folsom AR, Freudenheim JL, Giovannucci E, Goldbohm RA, Graham S, Harnack L, Horn-Ross PL, Krogh V, Leitzmann MF, McCullough ML, Miller AB, Rodriguez C, Rohan TE, Schatzkin A, Shore R, Virtanen M, Willett WC, Wolk A, Zeleniuch-Jacquotte A, Zhang SM, Hunter DJ (2006) Methods for pooling results of epidemiologic studies: the Pooling Project of Prospective Studies of Diet and Cancer. *Am J Epidemiol* 163(11):1053–1064. <https://doi.org/10.1093/aje/kwj127>
- Augustsson K, Skog K, Jägerstad M, Dickman PW, Steineck G (1999) Dietary heterocyclic amines and cancer of the colon, rectum, bladder, and kidney: a population-based study. *Lancet* 353(9154):703–707. [https://doi.org/10.1016/s0140-6736\(98\)06099-1](https://doi.org/10.1016/s0140-6736(98)06099-1)
- Cao W, Cai L, Rao JY, Pantuck A, Lu ML, Dalbagni G, Reuter V, Scher H, Cordon-Cardo C, Figlin RA, Belldegrun A, Zhang ZF (2005) Tobacco smoking, GSTP1 polymorphism, and bladder carcinoma. *Cancer* 104(11):2400–2408. <https://doi.org/10.1002/cncr.21446>
- Castelao JE, Yuan JM, Gago-Dominguez M, Skipper PL, Tannenbaum SR, Chan KK, Watson MA, Bell DA, Coetzee GA, Ross RK, Yu MC (2004) Carotenoids/vitamin C and smoking-related bladder cancer. *Int J Cancer* 110(3):417–423. <https://doi.org/10.1002/ijc.20104>
- Gaertner RR, Trpeski L, Johnson KC (2004) A case–control study of occupational risk factors for bladder cancer in Canada. *Cancer Causes Control* 15(10):1007–1019. <https://doi.org/10.1007/s10552-004-1448-7>
- Hemelt M, Hu Z, Zhong Z, Xie LP, Wong YC, Tam PC, Cheng KK, Ye Z, Bi X, Lu Q, Mao Y, Zhong WD, Zeegers MP (2010) Fluid intake and the risk of bladder cancer: results from the South and East China case-control study on bladder cancer. *Int J Cancer* 127(3):638–645. <https://doi.org/10.1002/ijc.25084>
- Karagas MR, Tosteson TD, Blum J, Morris JS, Baron JA, Klaue B (1998) Design of an epidemiologic study of drinking water arsenic exposure and skin and bladder cancer risk in a US population. *Environ Health Perspect* 106(Suppl 4):1047–1050. <https://doi.org/10.1289/ehp.98106s41047>
- Kellen E, Zeegers M, Paulussen A, Van Dongen M, Buntinx F (2006) Fruit consumption reduces the effect of smoking on bladder cancer risk. The Belgian case control study on bladder cancer. *Int J Cancer* 118(10):2572–2578. <https://doi.org/10.1002/ijc.21714>
- Polesel J, Bosetti C, di Maso M, Montella M, Libra M, Garbeglio A, Zucchetto A, Turati F, Talamini R, La Vecchia C,

- Serraino D (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(9):1151–1158. <https://doi.org/10.1007/s10552-014-0416-0>
16. Randi G, Pelucchi C, Negri E, Talamini R, Galeone C, Franceschi S, La Vecchia C (2007) Family history of urogenital cancers in patients with bladder, renal cell and prostate cancers. *Int J Cancer* 121(12):2748–2752. <https://doi.org/10.1002/ijc.23037>
 17. Shen M, Hung RJ, Brennan P, Malaveille C, Donato F, Placidi D, Carta A, Hautefeuille A, Boffetta P, Porru S (2003) Polymorphisms of the DNA repair genes XRCC1, XRCC3, XPD, interaction with environmental exposures, and bladder cancer risk in a case–control study in northern Italy. *Cancer Epidemiol Biomark Prev* 12(11 Pt 1):1234–1240
 18. Tang L, Zirpoli GR, Guru K, Moysich KB, Zhang Y, Ambrosone CB, McCann SE (2008) Consumption of raw cruciferous vegetables is inversely associated with bladder cancer risk. *Cancer Epidemiol Biomark Prev* 17(4):938–944. <https://doi.org/10.1158/1055-9965.epi-07-2502>
 19. Abbaoui B, Lucas CR, Riedl KM, Clinton SK, Mortazavi A (2018) Cruciferous vegetables, isothiocyanates, and bladder cancer prevention. *Mol Nutr Food Res* 62(18):e1800079. <https://doi.org/10.1002/mnfr.201800079>
 20. Boyer J, Liu RH (2004) Apple phytochemicals and their health benefits. *Nutr J* 3:5. <https://doi.org/10.1186/1475-2891-3-5>
 21. Büchner FL, Bueno-de-Mesquita HB, Ros MM, Kampman E, Egevad L, Overvad K, Raaschou-Nielsen O, Tjønneland A, Roswall N, Clavel-Chapelon F, Boutron-Ruault MC, Touillaud M, Chang-Claude J, Kaaks R, Boeing H, Weikert S, Trichopoulos A, Lagiou P, Trichopoulos D, Palli D, Sieri S, Vineis P, Tumino R, Panico S, Vrieling A, Peeters PH, van Gils CH, Lund E, Gram IT, Engeset D, Martínez C, Gonzalez CA, Larrañaga N, Ardanaz E, Navarro C, Rodríguez L, Manjer J, Ehrnström RA, Hallmans G, Ljungberg B, Allen NE, Roddam AW, Bingham S, Khaw KT, Slimani N, Boffetta P, Jenab M, Mouw T, Michaud DS, Kiemeny LA, Riboli E (2009) Consumption of vegetables and fruit and the risk of bladder cancer in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* 125(11):2643–2651. <https://doi.org/10.1002/ijc.24582>
 22. Sacerdote C, Matullo G, Polidoro S, Gamberini S, Piazza A, Karagas MR, Rolle L, De Stefanis P, Casetta G, Morabito F, Vineis P, Guarrera S (2007) Intake of fruits and vegetables and polymorphisms in DNA repair genes in bladder cancer. *Mutagenesis* 22(4):281–285. <https://doi.org/10.1093/mutage/gem014>
 23. Xenou D, Tzelves L, Terpos E, Stamatelopoulou K, Sergeantanis TN, Psaltopoulou T (2022) Consumption of fruits, vegetables and bladder cancer risk: a systematic review and meta-analysis of prospective cohort studies. *Nutr Cancer* 74(6):2003–2016. <https://doi.org/10.1080/01635581.2021.1985146>
 24. He C, Buongiorno LP, Wang W, Tang JCY, Miceli N, Taviano MF, Shan Y, Bao Y (2021) The inhibitory effect of sulforaphane on bladder cancer cell depends on GSH depletion-induced by Nrf2 translocation. *Molecules*. <https://doi.org/10.3390/molecules26164919>
 25. Azqueta A, Collins AR (2012) Carotenoids and DNA damage. *Mutat Res* 733(1–2):4–13. <https://doi.org/10.1016/j.mrfmmm.2012.03.005>
 26. Xu C, Zeng XT, Liu TZ, Zhang C, Yang ZH, Li S, Chen XY (2015) Fruits and vegetables intake and risk of bladder cancer: a PRISMA-compliant systematic review and dose-response meta-analysis of prospective cohort studies. *Medicine (Baltimore)* 94(17):e759. <https://doi.org/10.1097/md.0000000000000759>
 27. Brinkman MT, Karagas MR, Zens MS, Schned A, Reulen RC, Zeegers MP (2010) Minerals and vitamins and the risk of bladder cancer: results from the New Hampshire Study. *Cancer Causes Control* 21(4):609–619. <https://doi.org/10.1007/s10552-009-9490-0>
 28. Jochems SHJ, Reulen RC, van Osch FHM, Witlox WJA, Goossens ME, Brinkman M, Giles GG, Milne RL, van den Brandt PA, White E, Weiderpass E, Huybrechts I, Hémon B, Agudo A, Bueno-de-Mesquita B, Cheng KK, van Schooten FJ, Bryan RT, Wesselius A, Zeegers MP (2020) Fruit consumption and the risk of bladder cancer: a pooled analysis by the Bladder Cancer Epidemiology and Nutritional Determinants Study. *Int J Cancer* 147(8):2091–2100. <https://doi.org/10.1002/ijc.33008>
 29. Narii N, Sobue T, Zha L, Kitamura T, Sawada N, Iwasaki M, Inoue M, Yamaji T, Tsugane S (2022) Vegetable and fruit intake and the risk of bladder cancer: Japan Public Health Center-based prospective study. *Br J Cancer* 126(11):1647–1658. <https://doi.org/10.1038/s41416-022-01739-0>
 30. Gibson TM, Ferrucci LM, Tangrea JA, Schatzkin A (2010) Epidemiological and clinical studies of nutrition. *Semin Oncol* 37(3):282–296. <https://doi.org/10.1053/j.seminoncol.2010.05.011>
 31. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 372:n71. <https://doi.org/10.1136/bmj.n71>
 32. Wesselius A, Zeegers M (2017) Re: Lifestyle and bladder cancer prevention: no consistent evidence from cohort studies. *Eur J Epidemiol* 32(11):1037–1038. <https://doi.org/10.1007/s10654-017-0307-2>
 33. Krebs-Smith SM, Heimendinger J, Subar AF, Patterson BH, Pivonka E (1995) Using food frequency questionnaires to estimate fruit and vegetable intake: association between the number of questions and total intakes. *J Nutr Educ* 27(2):80–85. [https://doi.org/10.1016/S0022-3182\(12\)80346-3](https://doi.org/10.1016/S0022-3182(12)80346-3)
 34. Kristal AR, Peters U, Potter JD (2005) Is it time to abandon the food frequency questionnaire? *Cancer Epidemiol Biomark Prev* 14(12):2826–2828. <https://doi.org/10.1158/1055-9965.epi-12-ed1>
 35. Burger M, Catto JW, Dalbagni G, Grossman HB, Herr H, Karakiewicz P, Kassouf W, Kiemeny LA, La Vecchia C, Shariat S, Lotan Y (2013) Epidemiology and risk factors of urothelial bladder cancer. *Eur Urol* 63(2):234–241. <https://doi.org/10.1016/j.eururo.2012.07.033>
 36. Dugué PA, Brinkman MT, Hodge AM, Bassett JK, Bolton D, Longano A, Hopper JL, Southey MC, English DR, Milne RL, Giles GG (2018) Dietary intake of nutrients involved in one-carbon metabolism and risk of urothelial cell carcinoma: a prospective cohort study. *Int J Cancer* 143(2):298–306. <https://doi.org/10.1002/ijc.31319>
 37. Koebnick C, Michaud D, Moore SC, Park Y, Hollenbeck A, Ballard-Barbash R, Schatzkin A, Leitzmann MF (2008) Body mass index, physical activity, and bladder cancer in a large prospective study. *Cancer Epidemiol Biomark Prev* 17(5):1214–1221. <https://doi.org/10.1158/1055-9965.epi-08-0026>
 38. Madeb R, Messing EM (2004) Gender, racial and age differences in bladder cancer incidence and mortality. *Urol Oncol* 22(2):86–92. [https://doi.org/10.1016/s1078-1439\(03\)00139-x](https://doi.org/10.1016/s1078-1439(03)00139-x)
 39. Jiang X, Castela JE, Groshen S, Cortessis VK, Ross RK, Conti DV, Gago-Dominguez M (2007) Alcohol consumption and risk of bladder cancer in Los Angeles County. *Int J Cancer* 121(4):839–845. <https://doi.org/10.1002/ijc.22743>
 40. D’Avanzo B, La Vecchia C, Negri E, Decarli A, Benichou J (1995) Attributable risks for bladder cancer in northern Italy. *Ann Epidemiol* 5(6):427–431. [https://doi.org/10.1016/1047-2797\(95\)00057-7](https://doi.org/10.1016/1047-2797(95)00057-7)

41. Johnson KC, Mao Y, Argo J, Dubois S, Semenciw R, Lava J (1998) The National Enhanced Cancer Surveillance System: a case–control approach to environment-related cancer surveillance in Canada. *Environmetrics* 9(5):495–504. [https://doi.org/10.1002/\(SICI\)1099-095X\(199809/10\)9:5%3c495::AID-ENV318%3e3.0.CO;2-H](https://doi.org/10.1002/(SICI)1099-095X(199809/10)9:5%3c495::AID-ENV318%3e3.0.CO;2-H)
42. Steineck G, Hagman U, Gerhardsson M, Norell SE (1990) Vitamin A supplements, fried foods, fat and urothelial cancer. A case-referent study in Stockholm in 1985–87. *Int J Cancer* 45(6):1006–1011. <https://doi.org/10.1002/ijc.2910450604>
43. Di Maso M, Bosetti C, Taborelli M, Montella M, Libra M, Zucchetto A, Turati F, Parpinel M, Negri E, Tavani A, Serraino D, Ferraroni M, La Vecchia C, Polesel J (2016) Dietary water intake and bladder cancer risk: an Italian case–control study. *Cancer Epidemiol* 45:151–156. <https://doi.org/10.1016/j.canep.2016.09.015>

Authors and Affiliations

Iris W. A. Boot^{1,2,3}  · Anke Wesseliuss¹  · Sylvia H. J. Jochems¹ · Evan Y. W. Yu^{2,3,4} · Cristina Bosetti⁵ · Martina Taborelli⁶ · Stefano Porru^{7,8} · Angela Carta⁸ · Klaus Golka⁹ · Xuejuan Jiang^{10,11} · Mariana C. Stern¹⁰ · Eliane Kellen¹² · Hermann Pohlabein¹³ · Li Tang¹⁴ · Margaret R. Karagas¹⁵ · Zuo-Feng Zhang¹⁶ · Jack A. Taylor¹⁷ · Carlo La Vecchia¹⁸ · Maurice P. Zeegers¹

✉ Anke Wesseliuss
anke.wesseliuss@maastrichtuniversity.nl

¹ Department of Epidemiology, Maastricht University, P. Debeyelein 1, 6229 HA Maastricht, The Netherlands

² CAPHRI, Department of Epidemiology, Maastricht University Medical Centre+, Maastricht, The Netherlands

³ School of Nutrition and Translational Research in Metabolism, Maastricht University, 6229 ER Maastricht, The Netherlands

⁴ Key Laboratory of Environmental Medicine and Engineering of Ministry of Education, and Department of Epidemiology and Biostatistics, School of Public Health, Southeast University, Nanjing 210009, China

⁵ Unit of Cancer Epidemiology, Department of Oncology, IRCCS-Istituto di Ricerche Farmacologiche Mario Negri, Via Giuseppe La Masa 19, 20156 Milan, Italy

⁶ Unit of Cancer Epidemiology, CRO Aviano National Cancer Institute, Aviano, PN, Italy

⁷ Department of Diagnostics and Public Health, Section of Occupational Health, University of Verona, Verona, Italy

⁸ Interuniversity Research Center, Integrated Models for Prevention and Protection in Environmental and Occupational Health, MISTRAL, University of Brescia, University of Milano-Bicocca, University of Verona, Verona, Italy

⁹ Leibniz Research Centre for Working Environment and Human Factors, Sektion Lebenswissenschaften, Dortmund, Germany

¹⁰ Department of Preventive Medicine, University of Southern California, Los Angeles, CA, USA

¹¹ Department of Ophthalmology, University of Southern California, Los Angeles, CA, USA

¹² Leuven University Centre for Cancer Prevention (LUCK), Leuven, Belgium

¹³ Leibniz Institute for Prevention Research and Epidemiology-BIPS, Bremen, Germany

¹⁴ Department of Cancer Prevention and Control, Roswell Park Cancer Institute, Buffalo, NY, USA

¹⁵ Department of Epidemiology, Geisel School of Medicine at Dartmouth, Hanover, NH, USA

¹⁶ Departments of Epidemiology, UCLA Center for Environmental Genomics, Fielding School of Public Health, University of California, Los Angeles (UCLA), Los Angeles, CA, USA

¹⁷ Epidemiology Branch, and Epigenetic and Stem Cell Biology Laboratory, National Institute of Environmental Health Sciences, NIH, Research Triangle Park, NC, USA

¹⁸ Department of Clinical Medicine and Community Health, Università degli Studi di Milano, 20133 Milan, Italy