ARTICLE

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Vegetable and fruit intake and the risk of bladder cancer: Japan Public Health Center-based prospective study

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BACKGROUND: Vegetable and fruit consumption may have a protective effect against several types of cancer. However, evidence suggesting that increased intake of vegetables and fruits, their subtypes, or the antioxidant nutrients they contain in abundance decreases the risk of bladder cancer is limited.
METHODS: This study included 80,952 participants from the Japan Public Health Center-based Prospective Study, who responded to a food frequency questionnaire in a 5-year follow-up survey in 1995–1998 and were followed up until December 2015 to investigate the associations between intake of vegetables and fruits, their subtypes, or the antioxidant nutrients and bladder cancer risk using Cox proportional hazards regression models.
RESULTS: Within 1,287,514 person-years of follow-up, 401 bladder cancer cases (307 men and 94 women) were diagnosed. No association was found between intake of total vegetable and fruit, total vegetable, total fruit, subtypes of vegetables and fruits, or antioxidant nutrients and bladder cancer risk in both men and women, even in the analyses conducted among men stratified by smoking status.
CONCLUSIONS: In this population, the consumption of vegetables and fruits was not associated with the risk of bladder cancer.

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BACKGROUND

Bladder cancer is one of the top ten most common cancers worldwide, with ~550,000 new cases reported annually [1]. The global age-standardised incidence rate (ASR) is higher in men (9.6 per 100,000) than in women (2.4 per 100,000). The incidence of bladder cancer varies widely by region. The highest rates (ASR in men ≈ 20 per 100,000 per year and ASR in women ≈ 4.5 per 100,000 per year) were reported in Europe and North America, and approximately threefold lower rates were reported in Southeast Asia [1]. However, the incidence rates in Japan were higher than those in Southeast Asia (ASR in men 17.5 per 100,000 and ASR in women 3.7 per 100,000 in 2017) [2].

Given that some of the nutrients we take in from food are excreted in the urine, some foods and nutritional factors may contribute to bladder cancer risk [3]. Vegetables and fruits contain many antioxidants that potentially have anticarcinogenic properties, so consumption of vegetables and fruits may inhibit the development of several types of cancers. According to an expert panel of the World Cancer Research Fund (WCRF), the evidence suggesting that greater consumption of vegetables and fruits decreases the risk of bladder cancer is limited [4].

In particular, Japanese cohort studies have been conducted to investigate the association of intake of vegetables, fruits, or subtypes of vegetables or fruits with bladder cancer risk [5–8]. However, these studies showed inconsistent results and had several limitations. The food frequency questionnaire was fairly crude and simply assessed the food frequency to measure the dietary intake, without any information on portion size [5–8]. The reproducibility and validity of the questionnaire were not examined [5, 7]. Only the association of intakes of subtypes of vegetables or fruits with bladder cancer risk was examined, while that of total vegetables and fruits was not examined [6–8]. The Japan Public Health Center-based Prospective Study (JPHC Study) is a large-scale population-based prospective study in Japan to collect information on lifestyle habits from 140,420 people living in various parts of Japan and to clarify what lifestyle habits are related to the onset of diseases by tracking the onset of diseases for more than 20 years. Herein, we aimed to investigate the association between vegetable and fruit intake and bladder cancer risk in this large-scale population-based prospective study in Japan.

METHODS

Study cohort and participants

The JPHC Study conducted a baseline survey in 140,420 registered residents aged 40–69 years in 11 public health centres (PHCs) (Cohort I; Iwate, Akita, Nagano, Tokyo, Okinawa–Chubu, Cohort II; Niigata, Ibaraki, Osaka, Kochi, Nagasaki and Okinawa–Miyako) from 1990 to 1993. Details regarding the study design are reported elsewhere [9].

We enrolled participants who responded to a 5-year follow-up survey. We excluded participants registered in Tokyo ($n = 7097$) who did not have any information on cancer incidence and those registered in Osaka ($n = 16,427$) who had a different definition of the study population. Participants

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with foreign nationality ($n = 52$), who were relocated out of the study area before the date of response to the baseline survey ($n = 171$), with incorrect date of birth ($n = 4$), who were lost to follow-up ($n = 17$), and with duplicate registration ($n = 12$) were also excluded. After excluding those participants, 92,854 of 116,640 individuals (79.6%) aged 45 to 76 responded to the 5-year follow-up survey. We further excluded those who relocated out of the study areas before the follow-up start day ($n = 1661$) or with unknown relocation date ($n = 32$), who were diagnosed with any type of cancer before the start of follow-up ($n = 1824$) or had a history of cancer ($n = 554$), who had unknown ($n = 1045$) or extreme (lower and upper 2.5% percentile for each man and woman) intake of total energy ($n = 4386$), and who were ever smokers but did not indicate the number of cigarettes consumed per day ($n = 2396$). The final analytic cohort consisted of 37,061 men and 43,891 women.

Exposure definition

A self-administered food frequency questionnaire (FFQ) evaluated 138 food and beverage items consumed in the past year with three portion sizes (less than half, standard, and more than 1.5 times the standard portion size) and nine frequency categories (never, one to three times/month, one to two times/week, three to four times/week, five to six times/week, once/day, two to three times/day, four to six times/day and seven times/day). The frequency was multiplied by the relative portion size to calculate the daily consumption of each food items (g/day). The 30 vegetables and 16 fruits were categorised into total vegetables and fruits, total vegetables, green and yellow vegetables, cruciferous vegetables, green leafy vegetables, total fruits and citrus fruits. Details regarding the categories of vegetables and fruits are reported elsewhere [10, 11]. The daily consumption of antioxidant nutrients (retinol, α-carotene, β-carotene, lycopene, cryptoxanthin, vitamin C and vitamin E) was calculated using the Fifth Revised and Enlarged Edition of the Standard Tables of Food Composition in Japan [12].

To evaluate the validity and reproducibility of a self-administered FFQ, 215 participants (102 men and 113 women) from Cohort I and 350 participants (174 men and 176 women) from Cohort II participated in the validation studies voluntarily [13–15]. The validity of the FFQ was evaluated using 28- or 14-day dietary records as the gold standard. The FFQ was completed immediately or 3 months after the 28- or 14-day dietary records. The Spearman's correlation coefficients between estimates based on the FFQ and dietary records in men of Cohort I, men of Cohort II, women of Cohort I, and women of Cohort II follow; 0.22, 0.44, 0.32 and 0.47 for total vegetables, 0.41, 0.55, 0.23 and 0.29 for total fruits, 0.37, 0.43, 0.39, and 0.49 for retinol, 0.51, 0.47, 0.48 and 0.53 for α-carotene, 0.40, 0.46, 0.33 and 0.48 for β-carotene, 0.43, 0.48, 0.29 and 0.31 for cryptoxanthin, 0.43, 0.48, 0.30 and 0.47 for vitamin C, respectively [13–15]. The reproducibility of the FFQ was evaluated by repeating the FFQ at a 1-year interval. The Spearman's correlation coefficients in men of Cohort I, men of Cohort II, women of Cohort I and women of Cohort II follow; 0.62, 0.56, 0.53 and 0.59 for total vegetables, and 0.50, 0.57, 0.50 and 0.54 for total fruits [14, 16].

Follow-up and case identification

Participants were followed from the date of response to the 5-year follow-up survey until the date of any cancer diagnosis, death, emigration from Japan, or the end of follow-up (December 31, 2013, for Kochi and Nagasaki and December 31, 2015, for other PHC areas), whichever occurred first. Changes in residence status, including survival, were obtained annually through the residential registry in the municipality of each study area. In general, mortality data for residents included in the residential registry are sent to the Ministry of Health, Labour and Welfare and coded in the National Vital Statistics.

Cases of cancer were identified by active patient notification from the local major hospitals in the study areas and/or data linkage with the population-based cancer registries, with permission from each of the local governments. Death certificate information was used as a supplementary information source. Bladder cancer cases were defined by codes C67.0–67.9 of the International Classification of Diseases for Oncology, Third Edition. The morphology codes for the cases in the present study included 8000 (neoplasm), 8041 (small cell carcinoma), 8050 (papillary carcinoma), 8070 (squamous cell carcinoma), 8120 (transitional cell carcinoma), 8130 (papillary transitional cell carcinoma) and 8140 (adenocarcinoma). In all, 2.0% of bladder cancer cases in this study were ascertained from death certificates only. If two or more bladder cancers were diagnosed in one participant, the first bladder cancer was used for the analysis.

Statistical analysis

Cox proportional hazards model was used to calculate hazard ratios (HRs), 95% confidence intervals (CIs), and *P* trends for bladder cancer. Person-years of follow-up for each participant were calculated from the date of response to the 5-year follow-up survey and censored at the date of any cancer diagnosis, death, relocation out of the study area, or the end of follow-up (December 31, 2013, for Kochi and Nagasaki and December 31, 2015, for other PHC areas), whichever occurred first. The intake of vegetables, fruits and antioxidant nutrients was adjusted for total energy using the residual method, separately men and women [17], and categorised into quartiles with the lowest category as the reference. We conducted sex-specific evaluation because (1) there were sex differences in the intake of vegetables and fruits and the interaction between intake of vegetables and fruits and sex was significant (data not shown), (2) the incidence of bladder cancer differs greatly between males and females due to the large differences in the percentage of smokers and the amount of smoking in this cohort and (3) there is also substantial evidence that females present with more advanced disease stages at the primary diagnosis, which suggests that the development and detection of bladder cancer in males and females differs [18]. The multivariable analysis model was adjusted for age (continuous), study area (9 PHC areas), smoking status (never smoker, ever smoker, or unknown), duration of smoking (continuous), number of cigarettes per day (continuous), body mass index (<18.5, 18.5–25, 25–30 or >30 kg/m^2), history of diabetes mellitus (yes/no), family history of any cancer (yes/no), alcohol intake (<1 day/month, 1–3 days/month, >1 day/week and <150 g/week, or >1 day/week and >150 g/week), coffee intake (0, <150, 150–300 or >300 ml/day), physical activity (quintile of metabolic equivalents), fish intake (quartile of energy-adjusted fish intake), red meat intake (quartile of energy-adjusted red meat intake) and supplement intake (yes/no). An analysis was also conducted stratified by smoking status (never smoker or ever smoker) among men to investigate whether vegetable and fruit intake affect the bladder cancer risk, which is a potential cause of oxidative stress and inflammation. In addition, a sensitivity analysis was performed by excluding participants diagnosed with bladder cancer within 3 years or 10 years after the date of response to the 5-year follow-up survey.

All *P* values reported were two-sided, and the significance level was set at $P < 0.05$. All statistical analyses were performed using Stata version 16.0 (Stata Corporation, College Station, TX, USA).

RESULTS

Throughout the 1,287,514 person-years (median; 17.1 years) of follow-up, 401 participants (307 men and 94 women) were newly diagnosed with bladder cancer. The behaviour of neoplasms was determined in 399 participants, of whom 295 (74%) had malignant neoplasms and 104 (26%) had carcinoma in situ. Of the 401 participants, 352 (88%) had urothelial carcinoma, of whom 278 developed transitional cell carcinoma (M-8120) and 74 developed papillary transitional cell carcinoma (M-8130). In both men and women, participants who consumed more vegetables and fruits tended to be older and consume less red meat, alcohol, and coffee. They also have a lower prevalence of ever smokers, a lower number of cigarettes consumed per day, and a shorter duration of smoking. The prevalence of ever smokers among men was higher than that among women (Table 1).

The HRs and 95% CIs of bladder cancer incidence according to the quartiles of intake of vegetables and fruits, total vegetables, total fruits, and subgroups of vegetables or fruits are shown in Table 2. The crude incidence rate in men was 4.2 times higher than that in women (54.6 vs. 13.0 per 100,000 person-years). In the multivariable models, no significant association was observed in both men and women. In women, there was some evidence of a positive association when comparing the second quartile with the lowest quartile for vegetables [HR = 2.59 (95% CI: 1.36–4.93)], green-yellow vegetables [HR = 2.13 (95% CI: 1.13–4.03)], and cruciferous vegetables [HR = 2.08 (95% CI: 1.07–4.04)], although there was no association for the highest vs. the lowest and the trend were not significant. Excluding cases diagnosed with bladder cancer during the first 3 years or 10 years of follow-up did not change the results of the multivariable models.

Table 1. Baseline characteristics of participants according to sex-specific quartile of total vegetables and fruits intake.

	Quartiles (intake of total vegetables and fruits)				
	First	Second	Third	Fourth	P^b
Male (n = 37,061)					
Number of subjects	9266	9265	9265	9265	
Age (years), mean (SD)	55.8 (7.5)	56.6 (7.5)	57.7 (7.7)	59.2 (7.8)	<0.001
Body mass index (kg/m^2), mean (SD)	23.5 (3.0)	23.5 (2.9)	23.6 (2.9)	23.6 (2.8)	0.001
Ever smokers, %	79.1	74.1	70.8	65.3	<0.001
Number of cigarettes in ever smokers (per day), mean (SD)	18.6 (18.9)	16.6 (15.8)	15.4 (16.2)	13.7 (14.1)	<0.001
Duration of smoking in ever smokers (years), mean (SD)	24.8 (15.6)	23.3 (16.4)	22.2 (17.0)	20.9 (18.0)	<0.001
Family history of cancer (yes), %	17.1	17.1	17.1	18.3	0.101
History of diabetes mellitus (yes), %	5.8	6.0	7.4	8.9	<0.001
Regular alcohol drinker (once per week), %	78.1	71.7	64.6	53.5	<0.001
Coffee drinker (1 cup per day), %	32.5	32.1	31.4	28.3	<0.001
Intake of supplement (yes), %	7.2	8.8	9.5	11.7	<0.001
Dietary intake[a], median (IQR)					
Total vegetables and fruits (g/d)	150 (106–184)	268 (241–296)	389 (356–427)	600 (525–731)	<0.001
Red meat (g/d)	44 (25–72)	47 (28–72)	46 (28–70)	41 (24–62)	<0.001
Fish (g/d)	65 (40–99)	79 (53–111)	84 (58–120)	87 (59–122)	<0.001
Female (n = 43,891)					
Number of subjects	10,973	10,973	10,973	10,972	
Age (years), mean (SD)	56.8 (7.9)	57.6 (7.9)	58.2 (7.7)	58.7 (7.8)	<0.001
Body mass index (kg/m^2), mean (SD)	23.6 (3.3)	23.6 (3.2)	23.6 (3.2)	23.6 (3.1)	0.893
Ever smokers, %	10.8	6.7	5.7	4.8	<0.001
Number of cigarettes in ever smokers (per day), mean (SD)	1.5 (5.3)	0.9 (4.5)	0.7 (3.7)	0.6 (3.1)	<0.001
Duration of smoking in ever smokers (years), mean (SD)	2.7 (8.7)	1.6 (6.9)	1.4 (6.4)	1.2 (6.0)	<0.001
Family history of cancer (yes), %	14.3	16.2	17.7	17.5	<0.001
History of diabetes mellitus (yes), %	3.3	3.6	3.6	4.2	0.004
Regular alcohol drinker (once per week), %	14.7	11.9	10.2	8.4	<0.001
Coffee drinker (1cup per day), %	40.5	36.3	32.3	28.6	<0.001
Intake of supplement (yes), %	12.1	13.7	14.8	14.4	<0.001
Dietary intake[a], median (IQR)					
Total vegetables and fruits (g/d)	228 (174–267)	363 (332–392)	489 (454–528)	706 (631–835)	<0.001
Red meat (g/d)	48 (28–76)	43 (26–65)	38 (23–56)	31 (18–48)	<0.001
Fish (g/d)	67 (43–99)	79 (54–109)	80 (56–110)	77 (53–108)	<0.001

Means (standard deviation [SD]) or median (interquartile range [IQR]) for continuous variable and percentage [%] for categorical variables according to sex-specific quartile of energy-adjusted total vegetables and fruits intake.
[a]Dietary intake was adjusted for total energy intake using the residual method (sex-specific).
[b]Chi-square test for qualitative variables, Kruskal–Wallis test for continuous.

Vegetables and fruits contain numerous antioxidants with potentially anticarcinogenic properties. We investigated the association of carotenoids, vitamin C, and vitamin E concentrated in vegetables and fruits with bladder cancer risk. The HRs and 95% CIs of bladder cancer incidence according to the quartiles of the antioxidants are shown in Table 3. In multivariable models, no significant association was observed in both men and women. In women, there was some evidence of a positive association when comparing the third quartile with the lowest quartile [HR = 1.86 (95% CI: 1.05–3.30)] for α-carotene and the second [HR = 2.54 (95% CI: 1.30–4.99)] and the third quartile [HR = 2.12 (95% CI: 1.06-4.24)] with the lowest quartile for β-carotene although the association for the highest vs. the lowest and the trend were not significant. Excluding cases diagnosed with bladder cancer during the first 3 years of follow-up did not change the results of the multivariable models. In the sensitivity analysis excluding cases diagnosed with bladder cancer during the first 10 years, there was a positive association when comparing the highest quartile with the lowest quartile for retinol [HR = 1.73 (95% CI: 1.11–2.69), P trend = 0.02] in men but no association in women [HR = 1.42 (95% CI: 0.72–2.82), P trend = 0.65].

To examine the potential residual confounding and effect modification of smoking, we conducted stratified analysis by smoking status in men. The crude incidence rate in ever smokers was 1.7 times higher than that in never smokers (61.5 vs. 35.3 per 100,000 person-years). In multivariable models, the trend for green leafy vegetables for never smokers was marginally significant although there was no association for the highest vs. the lowest [HR = 2.17 (95% CI: 0.95–4.92)]. No significant associations were observed in total vegetables and fruits, vegetables, fruits, or subtypes of vegetables or fruit except green leafy vegetables with bladder cancer risk in either never or ever male smokers. We did not detect an interaction between each of the vegetables, fruits, and smoking status (Table 4). There was also no association

Table 2. Sex-specific hazard ratio (95% confidence interval) of bladder cancer according to the intake of vegetables and fruits by quartile.

	Intake by quartile				*P* trend
	First	Second	Third	Fourth	
Male (n = 37,061)					
Total vegetables and fruits					
Dietary intake, median (IQR)	150 (106–184)	268 (241–296)	389 (356–427)	600 (525–731)	
Person-years	140,856	142,814	140,752	138,281	
Number of cases	60	78	84	85	
IR per 100,000 person-years	42.6	54.6	59.7	61.5	
Model 1 HR (95% CI)	Ref	1.17 (0.84–1.64)	1.18 (0.84–1.64)	1.08 (0.77–1.51)	0.74
Model 2 HR (95% CI)	Ref	1.17 (0.83–1.65)	1.18 (0.84–1.66)	1.12 (0.79–1.58)	0.60
Total vegetables					
Dietary intake, median (IQR)	78 (55–95)	139 (125–153)	202 (184–222)	320 (278–399)	
Person-years	140,935	141,110	141,688	138,970	
Number of cases	67	73	90	77	
IR per 100,000 person-years	47.5	51.7	63.5	55.4	
Model 1 HR (95% CI)	Ref	1.01 (0.72–1.41)	1.15 (0.84–1.59)	0.92 (0.66–1.29)	0.82
Model 2 HR (95% CI)	Ref	0.98 (0.70–1.37)	1.12 (0.81–1.55)	0.92 (0.65–1.29)	0.80
Total fruits					
Dietary intake, median (IQR)	36 (20–53)	103 (87–120)	177 (156–201)	315 (265–410)	
Person-years	140,146	142,802	141,358	138,397	
Number of cases	62	72	96	77	
IR per 100,000 person-years	44.2	50.4	67.9	55.6	
Model 1 HR (95% CI)	Ref	1.03 (0.73–1.45)	1.30 (0.94–1.80)	0.96 (0.68–1.34)	0.89
Model 2 HR (95% CI)	Ref	1.03 (0.73–1.45)	1.34 (0.96–1.86)	1.00 (0.70–1.43)	0.67
Green and yellow vegetables					
Dietary intake, median (IQR)	25 (16–33)	56 (48–64)	90 (80–101)	153 (130–197)	
Person-years	139,110	141,163	142,169	140,261	
Number of cases	76	70	85	76	
IR per 100,000 person-years	54.6	49.6	59.8	54.2	
Model 1 HR (95% CI)	Ref	0.88 (0.63–1.22)	1.03 (0.75–1.40)	0.88 (0.64–1.21)	0.65
Model 2 HR (95% CI)	Ref	0.87 (0.62–1.20)	1.00 (0.73–1.37)	0.88 (0.63–1.23)	0.67
Cruciferous vegetables					
Dietary intake, median (IQR)	19 (13–25)	40 (35–45)	63 (57–70)	107 (91–137)	
Person-years	141,132	141,223	140,759	139,589	
Number of cases	66	73	83	85	
IR per 100,000 person-years	46.8	51.7	59.0	60.9	
Model 1 HR (95% CI)	Ref	1.02 (0.73–1.43)	1.07 (0.77–1.48)	0.98 (0.71–1.36)	0.96
Model 2 HR (95% CI)	Ref	1.00 (0.72–1.41)	1.06 (0.76–1.47)	0.98 (0.70–1.38)	0.98
Green leafy vegetables					
Dietary intake, median (IQR)	8 (5–11)	18 (16–21)	31 (27–36)	59 (49–78)	
Person-years	138,185	141,120	141,432	141,966	
Number of cases	60	76	75	96	
IR per 100,000 person-years	43.4	53.9	53.0	67.6	
Model 1 HR (95% CI)	Ref	1.20 (0.86–1.69)	1.13 (0.08–1.60)	1.33 (0.96–1.85)	0.13
Model 2 HR (95% CI)	Ref	1.17 (0.83–1.64)	1.11 (0.78–1.57)	1.34 (0.95–1.88)	0.13
Citrus fruits					
Dietary intake, median (IQR)	7 (3–13)	39 (30–47)	75 (65–87)	150 (120–208)	
Person-years	141,199	143,116	141,369	137,019	
Number of cases	61	75	92	79	
IR per 100,000 person-years	43.2	52.4	65.1	57.7	
Model 1 HR (95% CI)	Ref	1.13 (0.80–1.59)	1.35 (0.97–1.87)	1.07 (0.76–1.50)	0.53
Model 2 HR (95% CI)	Ref	1.14 (0.81–1.60)	1.35 (0.97–1.88)	1.11 (0.78–1.57)	0.41
Female (n = *43,891)*					
Total vegetables and fruits					
Dietary intake, median (IQR)	228 (174–267)	363 (332–392)	489 (454–528)	706 (631–835)	
Person-years	180,870	181,975	181,667	180,298	
Number of cases	15	26	23	30	

Table 2. continued

	Intake by quartile				*P* trend
	First	**Second**	**Third**	**Fourth**	
IR per 100,000 person-years	8.3	14.3	12.7	16.6	
Model 1 HR (95% CI)	Ref	1.58 (0.84–3.00)	1.35 (0.70–2.60)	1.67 (0.89–3.12)	0.19
Model 2 HR (95% CI)	Ref	1.60 (0.84–3.05)	1.36 (0.70–2.64)	1.68 (0.88–3.20)	0.21
Total vegetables					
Dietary intake, median (IQR)	104 (79–123)	170 (155–185)	235 (218–256)	358 (313–436)	
Person-years	179,396	180,938	182,330	182,147	
Number of cases	13	35	26	20	
IR per 100,000 person-years	7.2	19.3	14.3	11.0	
Model 1 HR (95% CI)	Ref	2.57 (1.36–4.86)	1.82 (0.93–3.54)	1.32 (0.65–2.67)	0.99
Model 2 HR (95% CI)	Ref	2.59 (1.36–4.93)	1.80 (0.91–3.54)	1.31 (0.64–2.69)	0.96
Total fruits					
Dietary intake, median (IQR)	76 (46-99)	160 (140–179)	244 (220–270)	404 (345–507)	
Person-years	181,485	182,553	181,901	178,870	
Number of cases	15	22	30	27	
IR per 100,000 person-years	8.3	12.1	16.5	15.1	
Model 1 HR (95% CI)	Ref	1.40 (0.72–2.71)	1.82 (0.96–3.44)	1.61 (0.84–3.10)	0.13
Model 2 HR (95% CI)	Ref	1.42 (0.73–2.77)	1.83 (0.96–3.49)	1.63 (0.83–3.17)	0.13
Green and yellow vegetables					
Dietary intake, median (IQR)	36 (26-45)	69 (61–76)	104 (94–115)	171 (146–214)	
Person-years	177,621	181,746	182,618	182,826	
Number of cases	14	31	25	24	
IR per 100,000 person-years	7.9	17.1	13.7	13.1	
Model 1 HR (95% CI)	Ref	2.14 (1.14–4.02)	1.63 (0.84–3.14)	1.48 (0.76–2.89)	0.57
Model 2 HR (95% CI)	Ref	2.13 (1.13–4.03)	1.60 (0.82–3.12)	1.47 (0.75–2.90)	0.62
Cruciferous vegetables					
Dietary intake, median (IQR)	26 (18–33)	50 (44–55)	74 (67–82)	121 (104–153)	
Person-years	179,140	181,424	182,575	181,670	
Number of cases	13	28	26	27	
IR per 100,000 person-years	7.3	15.4	14.2	14.9	
Model 1 HR (95% CI)	Ref	2.06 (1.07–3.98)	1.81 (0.93–3.53)	1.75 (0.90–3.41)	0.23
Model 2 HR (95% CI)	Ref	2.08 (1.07–4.04)	1.84 (0.93–3.62)	1.79 (0.91–3.54)	0.21
Green leafy vegetables					
Dietary intake, median (IQR)	12 (8-15)	24 (21–27)	39 (34–44)	70 (58–91)	
Person-years	175,753	180,709	183,145	185,202	
Number of cases	16	18	32	28	
IR per 100,000 person-years	9.1	10.0	17.5	15.1	
Model 1 HR (95% CI)	Ref	1.07 (0.54–2.11)	1.79 (0.98–3.29)	1.46 (0.78–2.73)	0.11
Model 2 HR (95% CI)	Ref	1.07 (0.54-2.11)	1.81 (0.98–3.35)	1.47 (0.78–2.79)	0.11
Citrus fruits					
Dietary intake, median (IQR)	20 (9-31)	62 (52–71)	105 (92–120)	204 (165–278)	
Person-years	182,907	184,835	181,630	175,439	
Number of cases	17	26	25	26	
IR per 100,000 person-years	9.3	14.1	13.8	14.8	
Model 1 HR (95% CI)	Ref	1.47 (0.79–2.72)	1.34 (0.72–2.51)	1.39 (0.74–2.61)	0.43
Model 2 HR (95% CI)	Ref	1.45 (0.78–2.70)	1.33 (0.71–2.51)	1.38 (0.73–2.60)	0.44

CI confidence interval, *HR* hazard ratio, *IR* incidence rate, *IQR* interquartile range, *Ref* reference.
Dietary intake was adjusted for total energy intake using the residual method (sex-specific), categorised into quartiles, and used in Cox proportional hazards regression model with the lowest category as the reference. Model 1: Cox proportional hazards regression models adjusted for age (continuous) and study area. Model 2 was further adjusted for smoking status (never smoker, ever smoker, or unknown); duration of smoking (continuous); the number of cigarettes per day (continuous); body mass index (30 kg/m^2), history of diabetes mellitus (yes/no), family history of any cancers (yes/no), Alcohol intake (1 day/week and 1 day/week and >150 g/week), coffee intake (0, 300 ml/day), physical activity (quintile of metabolic equivalents), fish intake (quartile of energy-adjusted fish intake), red meat intake (quartile of energy-adjusted red meat intake) and supplement intake (yes/no).

Table 3. Sex-specific hazard ratio (95% confidence interval) of bladder cancer according to the intake of nutrients by quartile.

	Intake by quartile				
	First	Second	Third	Fourth	*P* trend
Male (n = 37,061)					
Retinol					
Nutrient intake (μg/day)	105 (68–136)	261 (211–319)	522 (451–603)	987 (812–1319)	
Person-years	140,319	140,445	142,444	139,495	
Number of cases	70	73	74	90	
IR per 100,000 person-years	49.9	52.0	52.0	64.5	
Model 1 HR (95% CI)	Ref	1.10 (0.79–1.53)	1.15 (0.83–1.61)	1.42 (1.03–1.95)	0.03
Model 2 HR (95% CI)	Ref	1.08 (0.78–1.51)	1.10 (0.79–1.54)	1.35 (0.97–1.89)	0.09
α-carotene					
Nutrient intake (μg/day)	102 (59–143)	289 (241–342)	557 (475–654)	1,156 (928–1589)	
Person-years	139,913	142,031	141,117	139,642	
Number of cases	71	83	82	71	
IR per 100,000 person-years	50.7	58.4	58.1	50.8	
Model 1 HR (95% CI)	Ref	1.13 (0.82–1.55)	1.11 (0.80–1.52)	0.91 (0.65–1.27)	0.58
Model 2 HR (95% CI)	Ref	1.11 (0.81–1.54)	1.10 (0.79–1.52)	0.93 (0.66–1.32)	0.70
β-carotene					
Nutrient intake (μg/day)	1018 (726–1257)	1924 (1705–2162)	2976 (2673–3314)	5049 (4272–6523)	
Person-years	140,983	141,040	141,426	139,255	
Number of cases	72	74	75	86	
IR per 100,000 person-years	51.1	52.5	53.0	61.8	
Model 1 HR (95% CI)	Ref	0.95 (0.69–1.32)	0.91 (0.66–1.26)	0.98 (0.72–1.35)	0.87
Model 2 HR (95% CI)	Ref	0.93 (0.67–1.30)	0.90 (0.64–1.25)	1.01 (0.72–1.40)	0.99
Lycopene					
Nutrient intake (μg/day)	126 (51–198)	489 (373–644)	1750 (1,216-2,499)	5911 (4408–8699)	
Person-years	140,148	140,118	141,594	140,843	
Number of cases	76	72	95	64	
IR per 100,000 person-years	54.2	51.4	67.1	45.4	
Model 1 HR (95% CI)	Ref	0.94 (0.68–1.30)	1.17 (0.86–1.58)	0.84 (0.60–1.18)	0.67
Model 2 HR (95% CI)	Ref	0.93 (0.67–1.28)	1.16 (0.85–1.57)	0.82 (0.58–1.15)	0.57
Cryptoxanthin					
Nutrient intake (μg/day)	137 (76–217)	493 (401–587)	930 (803–1081)	1951 (1531–2839)	
Person-years	141,737	143,884	141,053	136,030	
Number of cases	65	72	76	94	
IR per 100,000 person-years	45.9	50.0	53.9	69.1	
Model 1 HR (95% CI)	Ref	1.03 (0.74–1.44)	1.04 (0.74–1.44)	1.18 (0.85–1.63)	0.32
Model 2 HR (95% CI)	Ref	1.04 (0.74–1.46)	1.04 (0.74–1.46)	1.25 (0.89–1.74)	0.21
Vitamin C					
Nutrient intake (mg/day)	52 (40–62)	88 (79–96)	125 (114–136)	189 (166–228)	
Person-years	142,375	142,225	141,318	136,786	
Number of cases	62	71	74	100	
IR per 100,000 person-years	43.5	49.9	52.4	73.1	
Model 1 HR (95% CI)	Ref	1.00 (0.71–1.41)	0.94 (0.67–1.33)	1.13 (0.82–1.57)	0.48
Model 2 HR (95% CI)	Ref	0.99 (0.70–1.39)	0.94 (0.66–1.33)	1.16 (0.82–1.64)	0.40
Vitamin E					
Nutrient intake (mg/day)	13 (11–15)	18 (17–19)	22 (21–23)	28 (26–32)	
Person-years	139,167	142,973	141,057	139,506	
Number of cases	75	77	73	82	
IR per 100,000 person-years	53.9	53.9	51.8	58.8	
Model 1 HR (95% CI)	Ref	0.91 (0.66–1.25)	0.84 (0.61–1.16)	0.90 (0.65–1.24)	0.45
Model 2 HR (95% CI)	Ref	0.86 (0.62–1.20)	0.80 (0.57–1.13)	0.87 (0.61–1.24)	0.43
Female (n = *43,891)*					
Retinol					
Nutrient intake (μg/day)	99 (68–125)	215 (180–259)	443 (375–516)	867 (711–1159)	
Person-years	180,151	180,157	182,684	181,819	
Number of cases	24	26	16	28	

Table 3. continued

	Intake by quartile				
	First	**Second**	**Third**	**Fourth**	***P* trend**
IR per 100,000 person-years	13.3	14.4	8.8	15.4	
Model 1 HR (95% CI)	Ref	1.11 (0.63–1.94)	0.70 (0.37–1.33)	1.24 (0.71–2.16)	0.75
Model 2 HR (95% CI)	Ref	1.08 (0.61–1.89)	0.67 (0.35–1.28)	1.18 (0.67–2.11)	0.90
α-carotene					
Nutrient intake (μg/day)	169 (98–237)	425 (361–495)	742 (652–849)	1393 (1142–1916)	
Person-years	178,690	182,393	182,756	180,971	
Number of cases	19	21	34	20	
IR per 100,000 person-years	10.6	11.5	18.6	11.1	
Model 1 HR (95% CI)	Ref	1.13 (0.61–2.10)	1.85 (1.05–3.25)	1.07 (0.57–2.03)	0.41
Model 2 HR (95% CI)	Ref	1.15 (0.61–2.15)	1.86 (1.05–3.30)	1.07 (0.56–2.06)	0.43
β-carotene					
Nutrient intake (μg/day)	1557 (1167–1860)	2638 (2385–2898)	3772 (3456–4132)	5982 (5166–7578)	
Person-years	178,771	181,461	183,243	181,335	
Number of cases	12	31	27	24	
IR per 100,000 person-years	6.7	17.1	14.7	13.2	
Model 1 HR (95% CI)	Ref	2.50 (1.28–4.87)	2.07 (1.05–4.09)	1.75 (0.87–3.52)	0.32
Model 2 HR (95% CI)	Ref	2.54 (1.30–4.99)	2.12 (1.06–4.24)	1.77 (0.87–3.62)	0.33
Lycopene					
Nutrient intake (μg/day)	181 (87–272)	586 (468–729)	1493 (1158–1995)	5060 (3658–7703)	
Person-years	180,921	180,711	181,895	181,283	
Number of cases	24	24	27	19	
IR per 100,000 person-years	13.3	13.3	14.8	10.5	
Model 1 HR (95% CI)	Ref	1.02 (0.58-1.80)	1.09 (0.62–1.90)	0.74 (0.40–1.36)	0.41
Model 2 HR (95% CI)	Ref	1.01 (0.57–1.80)	1.09 (0.62–1.91)	0.72 (0.39–1.32)	0.36
Cryptoxanthin					
Nutrient intake (μg/day)	307 (167–438)	790 (676–913)	1359 (1187–1562)	2834 (2232–3944)	
Person-years	184,002	184,772	181,627	174,409	
Number of cases	17	32	22	23	
IR per 100,000 person-years	9.2	17.3	12.1	13.2	
Model 1 HR (95% CI)	Ref	1.73 (0.96–3.13)	1.12 (0.59–2.13)	1.12 (0.59–2.15)	0.78
Model 2 HR (95% CI)	Ref	1.73 (0.96–3.15)	1.10 (0.58–2.11)	1.11 (0.57–2.13)	0.73
Vitamin C					
Nutrient intake (mg/day)	76 (60-88)	117 (108–126)	157 (146–170)	225 (202–263)	
Person-years	183,424	181,823	180,964	178,599	
Number of cases	19	21	29	25	
IR per 100,000 person-years	10.4	11.5	16.0	14.0	
Model 1 HR (95% CI)	Ref	0.97 (0.52–1.82)	1.23 (0.68–2.22)	0.96 (0.52–1.78)	0.92
Model 2 HR (95% CI)	Ref	0.98 (0.52–1.84)	1.21 (0.66–2.20)	0.94 (0.50–1.77)	0.99
Vitamin E					
Nutrient intake (mg/day)	16 (14–17)	20 (19–21)	23 (22–24)	29 (27–32)	
Person-years	176,880	181,170	184,128	182,632	
Number of cases	21	27	23	23	
IR per 100,000 person-years	11.9	14.9	12.5	12.6	
Model 1 HR (95% CI)	Ref	1.27 (0.72–2.26)	1.03 (0.56–1.87)	1.01 (0.55–1.86)	0.83
Model 2 HR (95% CI)	Ref	1.25 (0.69–2.24)	0.98 (0.53–1.81)	0.96 (0.51–1.80)	0.67

CI confidence interval, *HR* hazard ratio, *IR* incidence rate, *IQR* interquartile range, *Ref* reference.
Nutrient intake was adjusted for total energy intake using the residual method (sex-specific), categorised into quartiles, and used in Cox proportional hazards regression model with the lowest category as the reference. The nutrient intake in each quartile was shown as median (IQR). Model 1: Cox proportional hazards regression models adjusted for age (continuous) and study area. Model 2 was further adjusted for smoking status (never smoker, ever smoker, or unknown); duration of smoking (continuous); the number of cigarettes per day (continuous); body mass index (30 kg/m^2), history of diabetes mellitus (yes/no), family history of any cancers (yes/no), Alcohol intake (1 day/week and 1 day/week and >150 g/week), coffee intake (0, 300 ml/day), physical activity (quintile of metabolic equivalents), fish intake (quartile of energy-adjusted fish intake), red meat intake (quartile of energy-adjusted red meat intake), and supplement intake (yes/no).

Table 4. Hazard ratio (95% confidence interval) of bladder cancer according to the intake of vegetables and fruit by quartile stratified by smoking status among males.

	Intake by quartile					
	First	**Second**	**Third**	**Fourth**	***P* trend**	***P* interaction**
Total vegetables and fruits						
Male never smokers ($n = 10,066$)						
Dietary intake, median (IQR)	157 (113–187)	271 (243–298)	393 (359–429)	608 (528–744)		
Person-years	30,586	37,677	41,498	48,990		
Number of cases	6	15	17	18		
IR per 100,000 person-years	19.6	39.8	41.0	36.7		
Model 1 HR (95% CI)	Ref	1.88 (0.73–4.86)	1.75 (0.69–4.47)	1.42 (0.56–3.61)	0.79	
Model 2 HR (95% CI)	Ref	1.92 (0.73–5.01)	1.81 (0.70–4.70)	1.51 (0.57–3.97)	0.69	
Male ever smokers ($n = 26,337$)						
Dietary intake, median (IQR)	148 (105–183)	267 (240–294)	388 (354–426)	596 (523–721)		
Person-years	108,455	103,224	96,725	86,591		
Number of cases	53	62	65	63		
IR per 100,000 person-years	48.9	60.1	67.2	72.8		
Model 1 HR (95% CI)	Ref	1.12 (0.78–1.62)	1.16 (0.80–1.67)	1.11 (0.77–1.61)	0.57	
Model 2 HR (95% CI)	Ref	1.10 (0.76–1.59)	1.11 (0.77–1.62)	1.06 (0.72–1.56)	0.79	0.79
Total vegetables						
Male never smokers ($n = 10,066$)						
Dietary intake, median (IQR)	80 (58–96)	140 (126–154)	202 (186–224)	324 (279–408)		
Person-years	33,970	37,461	41,135	46,185		
Number of cases	6	14	20	16		
IR per 100,000 person-years	17.7	37.4	48.6	34.6		
Model 1 HR (95% CI)	Ref	1.90 (0.73–4.96)	2.41 (0.96–6.02)	1.63 (0.63–4.20)	0.41	
Model 2 HR (95% CI)	Ref	1.95 (0.74–5.14)	2.49 (0.98–6.34)	1.74 (0.66–4.61)	0.34	
Male ever smokers ($n = 26,337$)						
Dietary intake, median (IQR)	77 (54–95)	138 (125–152)	202 (184–222)	318 (277–393)		
Person-years	104,897	101,513	98,353	90,231		
Number of cases	59	59	67	58		
IR per 100,000 person-years	56.2	58.1	68.1	64.3		
Model 1 HR (95% CI)	Ref	0.96 (0.67–1.38)	1.04 (0.73–1.48)	0.89 (0.61–1.28)	0.64	
Model 2 HR (95% CI)	Ref	0.92 (0.64–1.33)	0.98 (0.68–1.40)	0.83 (0.57–1.21)	0.42	0.40
Total fruits						
Male never smokers ($n = 10,066$)						
Dietary intake, median (IQR)	39 (22–55)	104 (88–121)	178 (158–201)	324 (269–421)		
Person-years	30,379	37,644	42,517	48,211		
Number of cases	6	15	18	17		
IR per 100,000 person-years	19.8	39.8	42.3	35.3		
Model 1 HR (95% CI)	Ref	1.86 (0.72–4.81)	1.79 (0.70–4.55)	1.30 (0.50–3.38)	0.95	
Model 2 HR (95% CI)	Ref	1.81 (0.70–4.72)	1.73 (0.67–4.48)	1.32 (0.49–3.51)	0.90	
Male ever smokers ($n = 26,337$)						
Dietary intake, median (IQR)	36 (19–52)	103 (86–120)	176 (156–200)	311 (263–402)		
Person-years	108,110	103,045	96,535	87,304		
Number of cases	55	57	74	57		
IR per 100,000 person-years	50.9	55.3	76.7	65.3		
Model 1 HR (95% CI)	Ref	0.99 (0.68–1.44)	1.31 (0.92–1.86)	1.01 (0.69–1.47)	0.59	
Model 2 HR (95% CI)	Ref	0.96 (0.66–1.40)	1.28 (0.89–1.83)	0.96 (0.65–1.43)	0.76	0.67
Green and yellow vegetables						
Male never smokers ($n = 10,066$)						
Dietary intake, median (IQR)	26 (18–34)	57 (49–64)	91 (81–102)	155 (131–202)		
Person-years	33,613	37,272	40,838	47,028		

Table 4. continued

	Intake by quartile					
	First	Second	Third	Fourth	*P* trend	*P* interaction
Number of cases	8	13	20	15		
IR per 100,000 person-years	23.8	34.9	49.0	31.9		
Model 1 HR (95% CI)	Ref	1.41 (0.58–3.41)	2.00 (0.88–4.55)	1.28 (0.54–3.05)	0.52	
Model 2 HR (95% CI)	Ref	1.41 (0.58–3.43)	1.96 (0.85–4.54)	1.38 (0.57–3.36)	0.42	
Male ever smokers ($n = 26,337$)						
Dietary intake, median (IQR)	25 (16–33)	56 (48–64)	89 (80–100)	152 (129–194)		
Person-years	103,183	101,785	99,108	90,918		
Number of cases	66	56	62	59		
IR per 100,000 person-years	64.0	55.0	62.6	64.9		
Model 1 HR (95% CI)	Ref	0.83 (0.58–1.18)	0.91 (0.64–1.29)	0.87 (0.61–1.24)	0.56	
Model 2 HR (95% CI)	Ref	0.81 (0.56–1.16)	0.86 (0.60–1.23)	0.83 (0.57–1.19)	0.39	0.41
Cruciferous vegetables						
Male never smokers ($n = 10,066$)						
Dietary intake, median (IQR)	20 (13–25)	40 (36–46)	63 (57–71)	108 (91–138)		
Person-years	34,939	39,174	41,030	43,608		
Number of cases	11	13	14	18		
IR per 100,000 person-years	31.5	33.2	34.1	41.3		
Model 1 HR (95% CI)	Ref	0.94 (0.42–2.11)	0.89 (0.40–1.97)	0.97 (0.45–2.09)	0.94	
Model 2 HR (95% CI)	Ref	0.90 (0.40–2.03)	0.88 (0.39–1.99)	1.04 (0.47–2.29)	0.88	
Male ever smokers ($n = 26,337$)						
Dietary intake, median (IQR)	19 (12–25)	40 (35–45)	63 (56–70)	106 (90–136)		
Person-years	103,890	99,876	97,580	93,647		
Number of cases	53	59	67	64		
IR per 100,000 person-years	51.0	59.1	68.7	68.3		
Model 1 HR (95% CI)	Ref	1.10 (0.76–1.59)	1.17 (0.81–1.68)	1.03 (0.71–1.49)	0.84	
Model 2 HR (95% CI)	Ref	1.05 (0.72–1.52)	1.11 (0.77–1.61)	0.96 (0.66–1.41)	0.91	0.91
Green leafy vegetables						
Male never smokers ($n = 10,066$)						
Dietary intake, median (IQR)	8 (5–11)	18 (16–21)	31 (27–36)	59 (49–81)		
Person-years	35,961	37,659	39,447	45,684		
Number of cases	9	11	14	22		
IR per 100,000 person-years	25.0	29.2	35.5	48.2		
Model 1 HR (95% CI)	Ref	1.19 (0.49–2.87)	1.42 (0.61–3.31)	1.92 (0.87–4.23)	0.08	
Model 2 HR (95% CI)	Ref	1.24 (0.51–3.04)	1.51 (0.64–3.57)	2.17 (0.95–4.92)	0.05	
Male ever smokers ($n = 26,337$)						
Dietary intake, median (IQR)	8 (5–11)	18 (16–21)	31 (27–36)	59 (49–78)		
Person-years	99,722	101,414	99,620	94,238		
Number of cases	50	63	59	71		
IR per 100,000 person-years	50.1	62.1	59.2	75.3		
Model 1 HR (95% CI)	Ref	1.20 (0.82–1.74)	1.09 (0.75–1.60)	1.24 (0.86–1.80)	0.36	
Model 2 HR (95% CI)	Ref	1.15 (0.79–1.68)	1.04 (0.70–1.53)	1.18 (0.80–1.72)	0.54	0.83
Citrus fruits						
Male never smokers ($n = 10,066$)						
Dietary intake, median (IQR)	8 (4–13)	39 (30–48)	75 (65–87)	152 (120–212)		
Person-years	32,727	38,288	41,387	46,350		
Number of cases	7	13	13	23		
IR per 100,000 person-years	21.4	34.0	31.4	49.6		
Model 1 HR (95% CI)	Ref	1.46 (0.58–3.67)	1.29 (0.51–3.26)	1.64 (0.69–3.92)	0.33	
Model 2 HR (95% CI)	Ref	1.42 (0.56–3.58)	1.22 (0.48–3.13)	1.64 (0.68–3.99)	0.33	

Table 4. continued

	Intake by quartile					
	First	Second	Third	Fourth	*P* trend	*P* interaction
Male ever smokers ($n = 26,337$)						
Dietary intake, median (IQR)	7 (3–12)	39 (30–47)	75 (65–87)	148 (120–205)		
Person-years	106,662	102,923	97,864	87,545		
Number of cases	53	61	76	53		
IR per 100,000 person-years	49.7	59.3	77.7	60.5		
Model 1 HR (95% CI)	Ref	1.12 (0.77–1.62)	1.43 (1.01–2.04)	1.02 (0.69–1.50)	0.56	
Model 2 HR (95% CI)	Ref	1.11 (0.76–1.61)	1.39 (0.97–1.99)	0.98 (0.66–1.45)	0.75	0.21

CI confidence interval, *HR* hazard ratio, *IR* incidence rate, *IQR* interquartile range, *Ref* reference.
P for interaction was interaction by smoking status. Dietary intake was adjusted for total energy intake using the residual method (sex-specific), categorised into quartiles, and used in Cox proportional hazards regression model with the lowest category as the reference. Model 1: Cox proportional hazards regression models adjusted for age (continuous) and study area. Model 2 was further adjusted for smoking status (never smoker, ever smoker, or unknown); duration of smoking (continuous for ever smokers); the number of cigarettes per day (continuous for ever smokers); body mass index (30 kg/m^2), history of diabetes mellitus (yes/no), family history of any cancers (yes/no), Alcohol intake (1 day/week and 1 day/week and >150 g/week), coffee intake (0, 300 ml/day), physical activity (quintile of metabolic equivalents), fish intake (quartile of energy-adjusted fish intake), red meat intake (quartile of energy-adjusted red meat intake), and supplement intake (yes/no).

between intake of carotenoids such as α-carotene and β-carotene and incidence of bladder cancer in a stratified analysis by smoking status (Supplemental Table 1).

DISCUSSION

This population-based prospective cohort study in Japan found no association between intake of total vegetable and fruit, total vegetable, total fruit, subtypes of vegetables and fruits, or antioxidant nutrients and bladder cancer risk in both men and women. To our knowledge, this is the first study of a large general Japanese population to assess the association between vegetable and fruit consumption and bladder cancer risk by estimating the food and nutrient intake using a detailed and validated food frequency questionnaire. The major strengths of this study are its large general population of participants and prospective study design. A high response rate to the survey and a high follow-up rate are also strengths in minimising selection bias.

In the most recent report of WCRF/AICR, there was limited evidence to suggest that a high intake of fruits and vegetables reduces the risk of bladder cancer [4]. In previous studies, two meta-analyses of observational studies concluded that intake of vegetables and fruits was associated with a reduced risk of bladder cancer [19, 20]. However, other meta-analyses based on cohorts found no association between vegetable and fruit intake and bladder cancer risk [21, 22]. In a meta-analysis of cohort and case-control studies, there was an inverse association between fruit intake and the risk of bladder cancer. However, the association was not significant when the meta-analysis was restricted to cohort studies [23]. In this study, no association was found between the intake of vegetables and fruits and the risk of bladder cancer. This result is similar to that of previous cohort studies and meta-analyses [21, 22].

Contrary to our expectations, there was some evidence of an increased risk in the group with near median intakes of total vegetables, green-yellow vegetables, and cruciferous vegetables compared with the group with the lowest intake in women, although the *P* value for trend was not significant in this study. Each of these associations could be due to the confounding of unknown factors or measurement errors or a chance due to the small number of female bladder cancer cases. However, some results similar to ours have been reported. Park et al. [24] reported that total vegetables and yellow-orange vegetables (highest vs. lowest quartile) were inversely associated with the risk of invasive bladder cancer among women in the Multiethnic Cohort Study. However, the risk of invasive bladder cancer in the second quartile vs. the lowest quartile of intake of total vegetables, light green vegetables, dark green vegetables and cruciferous vegetables was slightly higher in women.

In a meta-analysis of cohort studies to assess the relationships of vegetable and fruit intake and bladder cancer risk [22], there was a slight increase in the risk of bladder cancer as total vegetable intake increased from 1 serving (80 g) to 2 servings (160 g) per day, and a nonlinear association was observed between a decrease in bladder cancer risk and total vegetable intake of more than 4 servings (320 g) per day in the nonlinear dose-response analysis. This trend was also observed for cruciferous vegetables, in which the risk of bladder cancer slightly increased as the intake of cruciferous vegetables increased from 1 to 3 servings per week (approximately 11.4–34.3 g per day) [22]. In this study, the median (interquartile range) intakes of total vegetables, green-yellow vegetables, or cruciferous vegetables for the lowest and second quartiles in women were 104 (79–123) and 170 (155–185), 36 (26–45) and 69 (61–76), or 26 (18–33) and 50 (44–55) g per day, respectively, which was close to the intake at which the increased risk was observed in the systematic review.

In this study, there was some evidence of an increased bladder cancer risk in the group with near median intakes of α-carotene and β-carotene. β-carotene is the most well-known carotenoid, known to quench singlet oxygen and a potent antioxidant [25]. Therefore, it was proposed that β-carotene may reduce the risk of cancer. A meta-analysis of cohort and case-control studies showed that a high intake of β-carotene was associated with a significantly lower risk of bladder cancer [26]. However, previous clinical trials failed to support these findings, and on the contrary, β-carotene supplementation marginally increased the risk of bladder cancer as reported in a meta-analysis of randomised controlled trials although the function of synthetic antioxidants may be different from that of natural antioxidants obtained from the diet [27].

Several studies have explained the biological mechanism underlying the harmful effects of beta-carotene [25, 27–31]. β-carotene has been reported to function as either an antioxidant or a prooxidant, depending on the environment in which it is present [31]. In the presence of chronic oxidative stress, such as smoking, it induces oxidative stress by generating reactive oxygen species or inhibiting the antioxidant system, which induces DNA damage [29]. In this study, the positive association found in women, but not in men, may be partially explained by the difference in bladder environment. There are sex differences in the anatomy of the bladder, urinary habits, hormone factors, and incidence of urinary tract infection and resultant cystitis [18, 32–34]. These differences in the bladder environment may alter an antioxidant or a prooxidant property of β-carotene, causing differences in its effects on the incidence of bladder cancer.

Smoking is a predominant risk factor for bladder cancer development. Since smokers suffer more oxidative damage from smoking than non-smokers, it can be hypothesised that antioxidants that reduce oxidative stress may derive more benefit from consuming fruits and vegetables [24, 35]. However, the effect of vegetables and fruits on bladder cancer risk among never and ever smokers was not consistent in previous cohort studies [24, 35–39]. In this study, we found no association between intake of vegetables and fruits and bladder cancer risk among never and ever male smokers and no significant interaction between smoking status and intake of vegetables and fruit.

There are several limitations to our study. First, although our study included a large population and had a long follow-up period, the statistical power was limited due to the small number of bladder cancer cases (307 men and 94 women). The limited sample size also made it difficult to look at tumour subtypes separately. Second, the intake of vegetables, fruits, and antioxidant nutrients was determined using a single point of self-administered FFQ, and the correlation coefficients to assess validity were moderate, which may have resulted in misclassification of exposure categories. Third, the possibility of residual confounding by smoking cannot be ruled out, and further adjustment for smoking may be necessary. Smoking is a predominant risk factor for bladder cancer development. In this study, there was a difference in smoking status, amount of smoking, and duration of smoking between participants with low and high vegetable and fruit intake. Fourth, some potential confounders were not adjusted in the multivariable analysis model. Although occupational carcinogen exposure is a risk factor for bladder cancer [1], this information was not collected in this study and not adjusted in the multivariable analysis model.

In conclusion, we found no evidence that the consumption of total vegetables and fruits, vegetables, and fruits reduces the risk of bladder cancer in this population.

DATA AVAILABILITY

For information on how to submit an application for gaining access to JPHC data and/or biospecimens, please follow the instructions at https://epi.ncc.go.jp/en/jphc/805/8155.html.

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AUTHOR CONTRIBUTIONS

NN, TS and LZ designed the work that led to the submission. NS and TS acquired the data. All authors participated in the interpretation of data. NN carried out the statistical analyses and drafted the manuscript. TS, LZ, TK, NS, M Iwasaki, M Inoue, TY and ST critically revised the manuscript. ST is the principal investigator of the JPHC Study. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted in compliance with the provisions of the Declaration of Helsinki. The study protocol was approved by the institutional review board of the National Cancer Center, Tokyo, Japan and by the Ethical Review Board of Osaka University, Osaka, Japan. The participants were informed of the study objectives, and those who completed the survey questionnaire were regarded as consenting to participation.

CONSENT TO PUBLISH

Not applicable.

ADDITIONAL INFORMATION

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