Table 1. Relative risk of lung cancer death associated with cigarette smoking, Three-Prefecture Cohort Study, Japan

Smoking status	No. subjects	Person-years	No. lung cancer deaths	Crude mortality rates	Relative risk† (95%CI)
Men					
Non-smokers	7 590	64 645	23	35.6	1.00
Former smokers	11 164	91 792	102	110.9	2.60 (1.65–4.10)
Current smokers	25 697	215 139	341	158.5	5.10 (3.34–7.79)
Women					
Non-smokers	36 884	321 170	79	24.6	1.00
Former smokers	1 630	13 258	13	98.1	2.94 (1.63–5.31)
Current smokers	5 188	42 931	40	93.2	3.66 (2.50–5.35)

†Adjusted for age and prefecture.

Table 2. Relative risk of lung cancer death by pack-years among current smokers, Three-Prefecture Cohort Study, Japan

Pack-years of smoking	No. subjects	Person-years	No. lung cancer deaths	Crude death rate	Relative risk† (95%CI)
Men‡					
<20	3 982	33 592	19	56.6	1.16 (0.72–1.88)
20–39	12 066	101 910	113	110.9	2.10 (1.62–2.71)
40–59	6 574	54 374	129	237.2	2.86 (2.23–3.65)
60 +	2 765	22 770	78	342.6	4.44 (3.34–5.89)
P for trend					<0.0001
Women§					
<20	3 136	26 212	12	45.8	1.75 (0.96–3.19)
20–39	1 545	12 642	15	118.7	3.92 (2.27–6.76)
40 +	397	3 157	10	316.8	7.22 (3.75–13.9)
P for trend					<0.0001

†Adjusted for age and prefecture. Reference category was non-smokers. ‡310 men were excluded because of missing data. §110 women were excluded because of missing data.

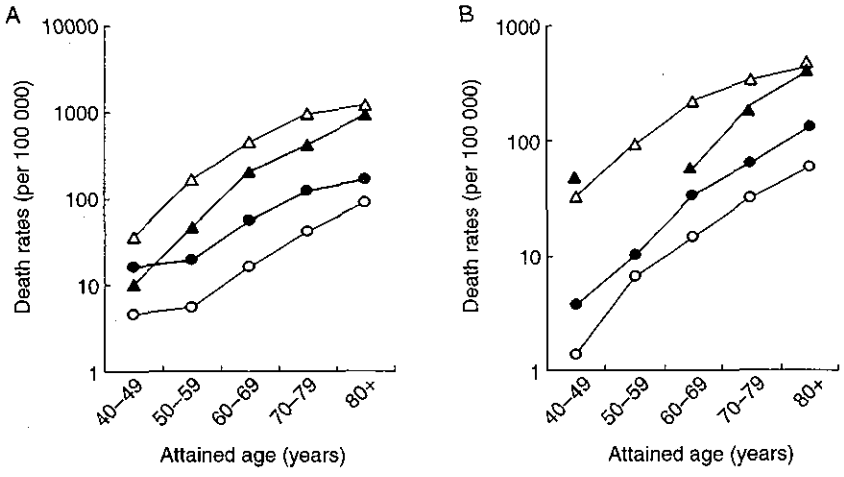

Fig. 1. Age-specific death rates due to lung cancer by attained age among current smokers and non-smokers in the Three-Prefecture cohort in Japan and Cancer Prevention Study II (CPS-II) in the USA. (a), Death rates of men; (b), death rates of women. (▲), Three-Prefecture cohort current smokers; (●), Three-Prefecture cohort nonsmokers; (△), CPS-II current smokers; (○), CPS-II non-smokers.

cigarette consumption for all age groups and for both men and women than current smokers in the USA. The differences ranged from 0.8 (aged 40–44 years) to 4.4 (aged 55–59 years) for men. Daily consumption of cigarettes in the youngest male age group showed the least difference. Japanese women constantly used approximately five fewer cigarettes per day in all age groups. The age-adjusted number of cigarettes per day for the Japanese and US cohorts were 21.5 and 24.8 for men, respectively, and 14.1 and 19.4 for women, respectively.

The mean number of years of smoking was slightly lower among Japanese men in all age groups than those in the USA (range 0.8–2.1) (Fig. 2b). Except for the youngest and oldest age groups, Japanese women had smoked for a much shorter time than comparable women in the USA. The range of differences was from 1.7 (aged 75–79 years) to 8.9 (aged 55–59 years). The age-adjusted years of smoking for the Japanese and US smokers were 37.1 and 38.6 years for men, respectively, and 26.8 and 34.2 years for women, respectively.

Japanese smokers in all age groups started smoking later than their counterparts in the USA, and this was especially true for women (Fig. 2c). While the age at initiation of smoking for Japanese women gradually became younger in recent birth

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Table 3. **Cumulative mortality and rate ratios for lung cancer among non-smokers and current smokers, Three-Prefecture Cohort Study in Japan compared to Cancer Prevention Study II in the USA**

	Non-smokers		Current smokers	
	Three-Prefecture	CPS-II	Three-Prefecture	CPS-II
Men				
Cumulative mortality rate (%)†	3.0	1.1	11.6	27.5
Rate ratio‡ (95%CI)	2.95 (1.79–4.87)	1.00	0.38 (0.32–0.41)	1.00
Women				
Cumulative mortality rate (%)†	1.9	0.8	5.3	11.6
Rate ratio‡ (95%CI)	2.10 (1.56–2.82)	1.00	0.42 (0.27–0.67)	1.00

Analysis restricted to first 6 years of follow-up to enhance comparability to Cancer Prevention Study II (CPS-II) data. †Cumulative mortality rates between 40 and 84 years. ‡Estimated based on Poisson regression model.

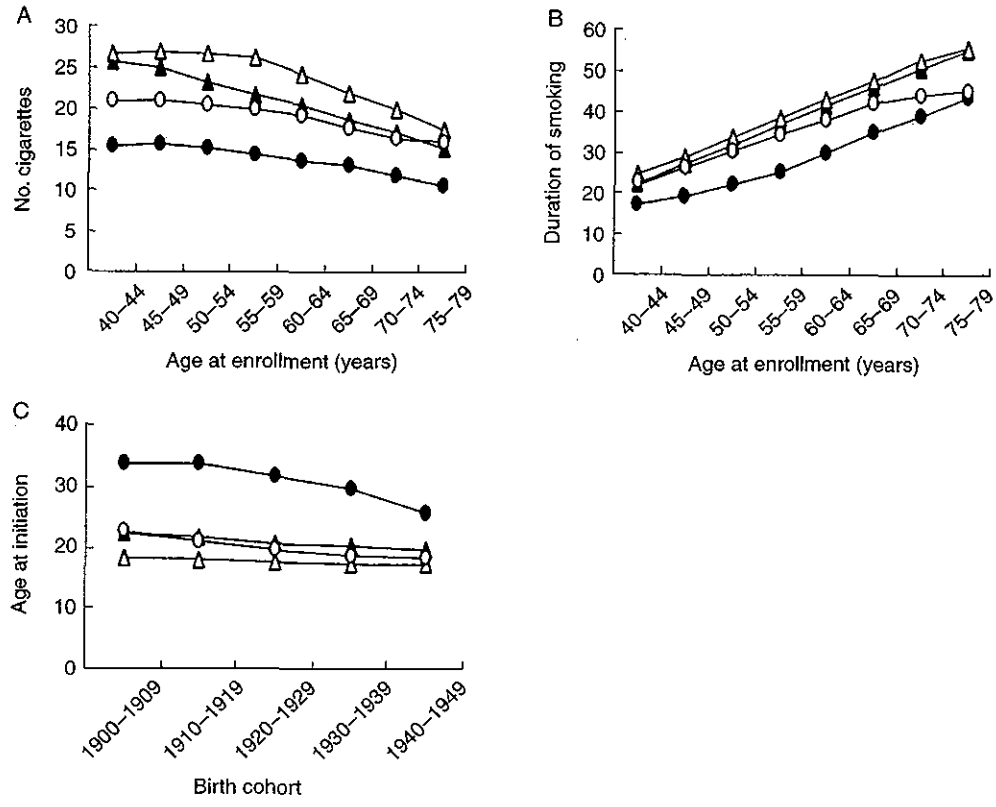

Fig. 2. Comparison of smoking patterns of current smokers at baseline between Three-Prefecture study in Japan and Cancer Prevention Study II (CPS-II) in the US. (a), Mean number of cigarettes smoked per day by age at enrolment; (b), mean duration of smoking by age at enrolment; (C), mean age of initiation of smoking by birth cohort. (▲), Three-Prefecture cohort men; (●), Three-Prefecture cohort women; (△), CPS-II men; (○), CPS-II women.

cohorts, they still began smoking much later than US women. The mean age at initiation of smoking among Japanese men in all birth cohorts was slightly older than those in the USA.

Finally, we calculated lung cancer death rates by years of smoking among current male smokers who had consumed 20 cigarettes per day (Table 4). Similar calculations for men who had smoked 40 cigarettes per day are not presented because there were too few of these men. We were unable to calculate lung cancer death rates in strata where no deaths occurred. For strata where calculations could be made, death rates of current Japanese smokers were lower than those in the USA. Rate ratios in all strata were less than 0.6. After controlling for age, duration of smoking and number of cigarettes smoked per day by the Poisson regression analysis, rate ratios of male Japanese current smokers relative to those in the USA was 0.34 (95%CI 0.27–0.43).

Discussion

The present large-scale, population-based prospective study confirmed an increased lung cancer risk among smokers, as compared with non-smokers, in Japan. The RR observed for Japanese smokers was lower than that observed in the USA. This finding is consistent with other studies conducted in Japan.[1–6] Comparison of death rates and exposure levels of current smokers in the two samples revealed one reason for the lower RR in Japan, namely, higher death rates among non-smokers

Table 4. Death rates by duration of smoking among current male smokers of 20 cigarettes per day, Three-Prefecture Study in Japan compared to the Cancer Prevention Study II in the USA

Attained age (years)	Three-Prefecture Duration*			CPS-II Duration†			Rate ratio Duration†		
	30–39	40–49	50 +	30–39	40–49	50 +	30–39	40–49	50 +
50–59	42.0	—	—	143.1	267.3	483.1	0.29	—	—
60–69	119.0	170.1	—	215.7	452.3	848.5	0.55	0.38	—
70–79	180.5	142.1	590.6	455.9	702.1	1149.0	0.40	0.20	0.51

†Duration of smoking was fixed at enrollment. —, no lung cancer deaths observed (Three-Prefecture cohort study), or no data available because of five or fewer deaths observed (Cancer Prevention Study II).

combined with lower death rates among smokers. A lower exposure level to smoking was responsible for the lower death rates among current smokers. However, even after adjustment for age, duration of smoking and daily cigarette consumption, male Japanese current smokers had a lower risk of lung cancer compared to those in the USA.

Death rates for non-smokers in all Japanese age groups were higher than those for non-smokers in the USA. The CPS-II used more detailed questions regarding smoking habits. For example, the CPS-II questionnaire clearly asked whether or not participants had smoked at least one cigarette per day for 1 year.[9] However, the questionnaire in our study did not specify the number of cigarettes or the duration of smoking. Therefore, the definition of non-smokers in the CPS-II was more strictly limited in terms of lifelong non-smokers, while non-smokers in our study might have included former smokers who had quit and not smoked for a long time. Such a difference in classification of non-smokers might have led to overestimation of death rates among Japanese non-smokers. Second-hand smoking might also have contributed to the difference. The prevalence of current smokers among Japanese subjects was higher than in the CPS-II. Among Japanese men, the prevalence was 58% for current smokers and 83% for ever smokers (ever smokers = current + former smokers); somewhat higher than the prevalence reported in the CPS-II (24% for white, male current smokers, 75% for white, male ever smokers, 36% for black, male current smokers, and 73% for black, male ever smokers).[9] Therefore, Japanese non-smokers might have had more opportunity to be exposed to environmental tobacco smoke (ETS). Furthermore, it was only in 2003 that Japanese law promoted the separation of smoking and non-smoking areas at the workplace and in public places. As well, since Japanese residences are small, Japanese non-smokers who had lived with parents or a spouse who smoked would have been exposed to concentrated tobacco carcinogens. Some, but not all, Japanese studies showed higher RR associated with spousal ETS,[11] and a pooled RR calculated from Japanese studies (1.41) was higher than the pooled RR calculated from US studies (1.19).[11] Therefore, until recently, Japanese non-smokers would have had a much higher cumulative exposure to ETS at home and in the workplace than their US counterparts.

Other risk factors, such as air pollution, radon and asbestos, do not offer a clear explanation for the observed differences. Several observational studies have shown an association between air pollution levels and lung cancer.[12,13] Even if a difference in air pollution levels exists between the two countries, it is unlikely that this small difference could account for the large difference in the risk of lung cancer among non-smokers given the only moderate association between air pollution and lung cancer.[14] The level of indoor radon in Japan, a known risk factor for lung cancer in Western countries[15] is much lower than in the USA.[16] Although asbestos consumption per capita was higher in Japan than in the USA during the mid-1970s,[17] it remains unknown whether low environmental exposure to asbestos (in contrast to heavy occupational exposure) causes lung cancer.[18]

In contrast to non-smokers, death rates among current smokers in our sample were lower than those observed in the CPS-II sample, regardless of age and sex. Because lung cancer risk and exposure level to smoking are clearly dose-related, the discrepancy in exposure levels among current smokers is probably a major factor explaining the difference in death rates among current smokers. However, considering lower exposure as a reason for the lower death rates among current smokers assumes that individuals with similar exposure levels have the same risk of lung cancer. However, the risk of lung cancer among male Japanese current smokers was lower than those in the USA, even after adjustment for age, duration of smoking and number of cigarettes smoked per day.

Although the difference in smoking patterns between the Japanese and US samples was greater among women than among men, the rate ratio for the current smokers was not very different between men and women. We have no clear explanation for this. However, the unit change in the lung cancer risk between Japanese female smokers and US female smokers with low levels of smoking exposure might not have the same magnitude as the unit change seen between Japanese male smokers and US male smokers with high levels of smoking exposure. Furthermore, Japanese women might under-report their smoking history. A single inquiry about smoking at baseline might not reflect the whole smoking history of individuals in either the Japanese or US samples.

Caution is advised when exposure levels to smoking are assessed, based on self-reported smoking history collected from a single questionnaire at the point of enrollment. Cigarette consumption per capita was much lower in Japan than in the USA from 1920 to 1970,[19] when the participants in these two cohorts were in adolescence to young adulthood. Furthermore, Japanese smokers experienced an extreme tobacco shortage during and immediately after World War II. It was not until the late 1970s that Japanese cigarette consumption per capita caught up with US consumption levels. Japanese participants classified in the same strata by smoking exposure undoubtedly experienced periods of cigarette shortage, and this bias toward overestimation of exposure may have produced spurious lower lung cancer death rates in our sample. Similarly, possible bias in the CPS-II sample may have included smokers who underreported usage of cigarettes due to strong social prohibitions to smoking in the USA.

Changes in tar content and the prevalence of filter-tipped cigarettes were also influential. The sales-weighted average yields of tar in the 1980s, and the reduction in tar levels during the 1960s and 1970s were similar in Japan and the USA.[20,21] Filter-tipped cigarettes were first marketed in the 1950s and their market share grew to more than 80% in the 1970s, reaching over 90% in both countries. However, as Stellmen *et al.* have noted, American manufactured cigarettes contain higher tobacco-specific nitrosamines than Japanese cigarettes.[22] Furthermore,

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charcoal filters, which remove certain compounds that inhibit lung clearance, are more widely used in Japanese cigarettes than American cigarettes.

Causes of death, other than lung cancer, might be influential in the estimation of lung cancer death rates among current smokers. Coronary heart disease (CHD) was the second leading cause of death among CPS-II smokers.[9] Premature death from CHD among CPS-II smokers might have led to somewhat lower lung cancer death rates in the USA. An increase in the discrepancy of lung cancer death rates among current smokers might have occurred, because death rates from CHD in Japan are not as high as in the USA.[23]

Other confounding factors, such as lifestyle or genetic factors, might also lower lung cancer death rates among Japanese smokers. The traditional Japanese diet, which is low in fat and high in several phytochemicals, might help decrease the risk of death due to lung cancer.[24–27] Deletion-type polymorphism CYP2A6, the principal enzyme in the metabolic activation of tobacco-specific nitrosamines, was found to be inversely associated with lung cancer among Japanese male smokers.[28] It has been demonstrated that the frequency of occurrence of this variant is higher amongst Japanese than among Caucasians.[29] However, caution is required, because diet and the odds of having CYP2A6 can be assumed to be constants (i.e. would be equally likely to affect non-smokers) and non-smokers presented the opposite pattern to current smokers.

Another potential explanation is different histological distribution of lung cancer between American and Japanese populations.[30] Adenocarcinoma, which is less strongly related to smoking than squamous cell carcinoma,[2] contributes to a larger proportion of Japanese lung cancer than US lung cancers. The relatively lower incidence of squamous cell carcinoma among Japanese smokers would reduce the overall Japanese lung cancer incidence for the same level of exposure to smoking as in the US cohort.

Generally, in Western countries non-smokers have a higher socioeconomic status than smokers. People with a high socioeconomic status tend to have more health conscious lifestyles, such as a higher intake of fruits and vegetables, as well as lower occupational exposures to other factors, such as asbestos. In the USA, the socioeconomic gap between smokers and non-smokers is much larger due to a strong societal antismoking campaign. This larger disparity of background risk factors resulted in a larger difference of lung cancer mortality between US non-smokers and smokers, as compared with Japanese non-smokers and smokers.

Finally, the comparability of the Japanese and US samples should be considered. A potential advantage was that both studies were conducted using a prospective design during approximately the same time period. Dates of birth of participants covered approximately the same years. Because cigarette types, such as non-filtered versus filtered cigarettes changed similarly in both the USA and Japan from the 1950s to the 1970s,[31] different study periods or birth cohorts might have weakened the comparability, especially in terms of exposure. In addition, lung cancer deaths were basically diagnosed by the same ICD-9 codes. Lung cancer deaths were determined based on death certificates for the US sample, and the Japanese sample lung cancer deaths were determined using the cancer registry, which was based on death certificate data. Death certificates were usually considered complete both in the US and Japan. As well, the cause of death was also considered to have been identified with reasonable accuracy. In 1988, the percentage of deaths with no classifiable diagnosis, including unknown cause of morbidity and mortality (ICD-9: 780–799) was 3.9% for Japan and 1.4% for USA. Therefore, both studies appeared to be equal in their precision of determining lung cancer deaths. Finally, follow-up periods were restricted to 6 years in both studies. However, over this relatively short time interval, there were too few deaths among the Japanese cohort to produce stable and informative estimates of death rates, especially at high exposure levels. To solve this problem, further investigation with samples as large as the CPS-II sample, or the pooling of several studies, are needed.

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Original Article

Foods and beverages in relation to urothelial cancer: Case-control study in Japan

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Abstract

Background: The roles of several foods and beverages in the development of bladder cancer remain unclear.

Methods: We undertook a hospital-based case-control study at Aichi Cancer Center Hospital, Japan. Subjects included 124 men and women (bladder cancer cases) with newly diagnosed cancers of the renal pelvis ($n = 5$), ureter ($n = 6$) or bladder ($n = 113$) and 620 age- and sex-matched, cancer-free outpatients (controls) presenting at the hospital in the period from 1994 to 2000. Smoking-adjusted odds ratios (OR) were estimated to assess the strength of associations between self-reported intake of foods or drinks and bladder cancer risk, using conditional logistic models.

Results: We found a decreased risk in relation to frequent intake of green–yellow vegetables; the OR for the highest intake score compared with the lowest was 0.54 (95% confidence interval [CI] 0.29–0.99). The OR for carrot intake of ≥5 times/week compared with ≤1–3 times/month was 0.41 (95% CI 0.16–1.01) and a decreasing risk with increasing consumption of green vegetables was also detected (P for trend = 0.063). Inverse associations between black tea, eggs and meat and risk were also suggested, whereas moderate drinkers of green tea (5–9 cups/day) showed an elevated risk. Coffee and milk consumption did not appear to exert any influence.

Conclusions: Those with an increased risk of bladder cancer, such as smokers, may benefit from increasing their consumption of green–yellow vegetables.

Key words beverages, bladder neoplasms, case-control studies, diet, vegetables.

Introduction

The incidence of bladder cancer has generally been increasing in industrialized countries, including Japan.[1] The consumption of foods and beverages has long been related to the risk of this cancer in addition to smoking, occupational exposure to carcinogenic chemicals and infection with *Schistosoma hematobium*.[2] In 1997, the World Cancer Research Fund and the American Institute for Cancer Research thoroughly reviewed epidemiological studies and concluded that diets high in vegetables and fruits probably protect against bladder cancer.[2]

Nevertheless, the roles of several foods and drinks in the development of bladder cancer remain unknown or controversial. Higher consumption of coffee may increase the risk,[2] but data from Asian populations are quite limited.[3–5] Some epidemiological studies have shown that diets rich in meats may increase the risk,[6–8] whereas others have reported an inverse association.[9–11] Soybean products and green tea contain anticarcinogenic components, such as isoflavones[12,13] and polyphenols,[14] respectively, and may reduce cancer risk. Nevertheless, the evidence relating the consumption of soy foods[4,11]

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or green tea[4,5,11,15] to the risk of bladder cancer is equivocal. Contrary to expectation, one study in Taiwan revealed a three-fold elevation in oolong tea drinkers.[5]

To further address these issues regarding diet and bladder cancer, we undertook a case-control study using data from the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC).

Methods

Study subjects and data collection

The HERPACC was initiated in Aichi Cancer Center Hospital, Nagoya, in 1988, with information on lifestyle factors routinely collected from all first-visit outpatients, using a self-administered questionnaire checked by a trained interviewer. Each patient was asked about his or her lifestyle when healthy or before the current symptoms developed. The hospital is located in the central part of Japan and more than 95% of the outpatients reside in the Tokai area, which has a population of 15 million. The questionnaire data are loaded into the HERPACC database and routinely linked with the hospital cancer registry system to update the data on cancer incidence. The ethics board of the prefectural government reviewed and approved the protocol for this project. Details of the questionnaire and data collection procedures have been described elsewhere.[16,17]

The present study is based on data collected between January 1994 and December 2000 because the Aichi Cancer Center Hospital started its urology service in 1994. Among all first-visit outpatients during this period ($n = 43\,975$), the questionnaire was given to 39 144 (89.0%). The remaining 4831 (11.0%) were excluded because they were too young (<18 years) or too ill to fill out the form, because of the absence of an interviewer or due to a consultation visit by someone other than the patient themself. Of the 39 144 outpatients, 38 798 (99.1%) provided adequate responses to the questionnaire. A total of 8983 cancer patients (23.2% of the 38 798 respondents) were diagnosed and entered into the hospital-based cancer registry system.

Among them, all patients with cancers of the renal pelvis ($n = 5$), ureter ($n = 6$) or bladder ($n = 113$; International Statistical Classification of Diseases and Related Health Problems, 10th Revision [ICD-10]: C65–C67[18]), newly (±1 years of the first visit) and diagnosed histopathologically were deemed eligible cases. Almost all the cancers ($n = 117$; 94.4%) were diagnosed within ± 2 months of the first visit. Transitional cell carcinoma accounted for 90.3% of cases ($n = 112$), followed by adenocarcinoma (3.2%; $n = 4$) and others (6.5%; $n = 8$). The distributions of TNM classification clinically staged[19,20] at the first presentation were as follows. In patients with cancer of the bladder, Tis $n = 5$, Ta $n = 16$, T1 $n = 40$, T2 $n = 16$, T3 $n = 18$, T4 $n = 5$ and TX $n = 13$; N0 $n = 87$, N1 $n = 4$, N2 $n = 6$ and NX $n = 16$; and M0 $n = 84$, M1 $n = 9$ and MX $n = 20$. In those with cancers of the pelvis and ureter, T1 $n = 1$, T2 $n = 2$, T3 $n = 4$ and TX $n = 4$; N0 $n = 6$, N1 $n = 1$, N2 $n = 1$ and NX $n = 3$; and M0 $n = 5$, M1 $n = 3$ and MX $n = 3$. We hereafter refer to all lesions as 'bladder cancer' for simplicity because 91.1% of patients had a bladder tumor.

We randomly selected five controls for each case from among the 29 815 cancer-free individuals, matching for age (5-year strata), sex and year of first visit. Those with a prior history of cancer were excluded. Consequently, 124 cases and 620 controls were included in the present study.

The HERPACC questionnaire applied included items on demographic characteristics, family and individual medical history, smoking and drinking habits, regular physical exercise and reproductive history, as well as consumption of selected foods and beverages. For most foods, the questionnaire elicited average intake frequency. The questions had five possible responses: almost never, 1–3 times/month, 1–2 times/week, 3–4 times/week and ≥5 times/week, except for fruit (almost never, occasionally, 3–4 times/week and almost every day) and miso soup and milk (almost never, occasionally, once per day and ≥2 times/day). Information on the intake frequency of alcoholic beverages, green tea, coffee and black tea was also collected (almost never, occasionally and almost every day). We further asked about consumption (per day) for daily drinkers of these beverages. Alcohol consumption was recorded in the Japanese measure ('gou'), equivalent to 22 g ethanol.

Statistical analysis

We combined men and women in the analysis because of the small number of female cases ($n = 24$). Cases and controls were categorized by consumption of foods or beverages. To assess associations of food groups with bladder cancer risk, we calculated intake scores (estimates of weekly frequency) for green–yellow vegetables, other vegetables and meats. For each food item in a group, intake frequency of almost never, 1–3 times/month, 1–2 times/week, 3–4 times/week and ≥5 times/week was scored as 0, 0.5, 1.5, 3.5 and 5, respectively. This individual score was then summed over all the items in one food group and subjects were divided into three groups according to the total score (0.0–4.9, 5.0–9.9 and ≥10.0).

Odds ratios (OR) and their 95% confidence intervals (CI) were estimated to assess the strength of the associations between intakes of foods or food groups and bladder cancer risk. We also computed OR for season of questionnaire administration, family history of bladder cancer and cumulative consumption of cigarettes. Given the matched design of this case-control study, we applied conditional logistic models[21] to estimate the OR adjusted for smoking habits (cumulative consumption of cigarettes: 0, 1–19, 20–39, 40–59 and ≥60 pack-years) and matching variables. However, in the analysis by smoking status (never or ever), we used unconditional logistic models,[22] including age (as a continuous variable), sex, year of first visit (1994–1996, 1997–1998 and 1999–2000) and cumulative consumption of cigarettes (1–19, 20–39, 40–59 and ≥60 pack-years for ever smokers). The OR for ever smokers compared with non-smokers by consumption level of green–yellow vegetables were estimated using unconditional logistic models with adjustment for age, sex and year of first visit. We also performed multivariate analysis simultaneously considering the risk or protective factors and matching variables in conditional logistic models.

Missing values in smoking habits were replaced by mode values in cases or controls. Only 1.3% of cases and controls lacked such information. To test for a linear trend across the exposure levels, we coded each level as 0, 1, 2, . . . and then included it in the logistic model as a single variable.[23] The proportion of bladder cancers preventable by a higher consumption of green–yellow vegetables was estimated as proposed by Miettinen.[24]

The SAS, release 8.2 (SAS Institute Inc., Cary, NC, USA),[25] was used to perform the statistical analysis.

Results

Table 1 shows the distribution of cases and controls according to background characteristics; age, sex and year of first visit were exactly matched between cases and controls. Mean (± SD) age was 61.9 ± 10.6 years for both cases and controls. The season of questionnaire

Table 1 Characteristics of the 124 bladder cancer cases and 620 controls

Characteristic	Cases		Controls		OR†	95% CI
	n	%	*n*	%		
Age (years)						
20–29	2	1.6	10	1.6		
30–39	1	0.8	5	0.8		
40–49	9	7.3	45	7.3		
50–59	35	28.2	175	28.2		
60–69	46	37.1	230	37.1		
70–79	31	25.0	155	25.0		
Sex						
Male	100	80.6	500	80.6		
Female	24	19.4	120	19.4		
Year of first visit						
1994–1996	47	37.9	235	37.9		
1997–1998	32	25.8	160	25.8		
1999–2000	45	36.3	225	36.3		
Season of questionnaire administration						
Spring	25	20.2	157	25.3	1.00	
Summer	36	29.0	180	29.0	1.23	0.73–2.09
Autumn	36	29.0	147	23.7	1.48	0.87–2.52
Winter	27	21.8	136	21.9	1.23	0.69–2.20
Family history of bladder cancer‡						
No	121	97.6	615	99.2	1.00	
Yes	3	2.4	5	0.8	2.58	0.73–9.18
Cumulative consumption of cigarettes (pack-years)						
0	31	25.6	223	36.4	1.00	
1–19	15	12.4	94	15.3	1.30	0.65–2.59
20–39	23	19.0	130	21.2	1.58	0.82–3.05
40–59	33	27.3	98	16.0	2.90	1.55–5.42***
≥60	19	15.7	68	11.1	2.41	1.21–4.78*
						P for trend = 0.0009

*$P < 0.05$, ***$P < 0.001$. †Adjusted for age, sex and year of first visit. ‡Family history involving parents or siblings. OR, odds ratio; CI, confidence interval.

administration was similarly distributed in cases and controls. Those with a family history of bladder cancer demonstrated an increased risk, but this did not reach statistical significance (OR 2.58; 95% CI 0.73–9.18). As expected, cigarette smoking was strongly related to bladder cancer risk: the greater the cumulative consumption, the higher the OR (P for trend = 0.0009). The OR were 2.90 (95% CI 1.55–5.42) for 40–59 pack-years and 2.41 (95% CI 1.21–4.78) for 60 pack-years or more. Thus, we treated smoking as a confounding factor in the following analysis.

Those who consumed five to nine cups of green tea daily, compared with non-daily drinkers, were at an increased risk of bladder cancer (Table 2; OR 2.67; 95% CI 1.44–4.94). However, this was not the case with consumption of 10 cups/day or more. Daily drinking of black tea showed a somewhat low OR (0.16; 95% CI 0.02–1.14). No significant association was found between alcoholic beverages or coffee and bladder cancer risk.

The most frequent consumption of carrots tended to be associated with a reduced risk (Table 3): the OR for intake 5 times/week or more compared with 1–3 times/month or less was 0.41 (95% CI 0.16–1.01). There was also some suggestion of a decreased risk with an increasing consumption of green vegetables (P for trend = 0.063). Frequency of egg intake was negatively associated with the risk of bladder cancer: the OR across intake levels were 0.77, 0.82 and 0.50 (P for trend = 0.030). Other individual foods, including milk, neither enhanced nor reduced the risk significantly.

For food groups (Table 4), a reduction in bladder cancer risk was linked to the frequent consumption of green–yellow vegetables (intake score ≥10.0 *vs* 0.0–4.9; OR 0.54, 95% CI 0.29–0.99), but not that of other vegetables. We also observed a decreasing risk with increasing intake scores for meat as a group (P for trend = 0.023).

Protective effects of green–yellow vegetables were similarly observed in both non-smokers and smokers, the OR for intake scores of ≥10.0 compared with 0.0–4.9 being 0.50 (95% CI 0.18–1.40) in never smokers and 0.51 (95% CI 0.22–1.17) in ex- or current

Table 2 Odds ratios for bladder cancer by beverage consumption

Beverage	Cases		Controls		OR†	95% CI
	n	%	*n*	%		
Alcoholic beverages						
Almost never	48	38.7	266	42.9	1.00	
Ex-drinkers	14	11.3	48	7.7	1.33	0.68–2.59
Current drinkers (Japanese drinks/day)‡						
<1.0	28	22.6	149	24.0	1.00	0.60–1.65
1.0–1.9	15	12.1	73	11.8	0.96	0.50–1.83
2.0–2.9	8	6.5	48	7.7	0.65	0.29–1.46
≥3.0	11	8.9	36	5.8	1.19	0.56–2.51
						P for trend = 0.97††
Green tea (cups/day)						
<1	14	11.3	115	18.6	1.00	
1–4	42	33.9	260	42.0	1.40	0.74–2.62
5–9	59	47.6	178	28.8	2.67	1.44–4.94**
≥10	9	7.3	66	10.7	1.18	0.49–2.84
						P for trend = 0.024
Coffee (cups/day)						
Almost never	26	21.0	145	23.4	1.00	
Occasionally	23	18.5	123	19.8	0.93	0.52–1.66
1	28	22.6	163	26.3	0.82	0.47–1.44
2	26	21.0	113	18.2	1.07	0.59–1.94
≥3	21	16.9	76	12.3	1.14	0.58–2.23
						P for trend = 0.68
Black tea (cups/day)						
Almost never	98	79.0	453	73.1	1.00	
Occasionally	25	20.2	132	21.3	0.96	0.60–1.53
≥1	1	0.8	35	5.6	0.16	0.02–1.14§
						P for trend = 0.12

§$P < 0.10$, **$P < 0.01$. †Adjusted for age, sex, year of first visit, and cumulative consumption of cigarettes. ‡One Japanese drink ('gou') is equivalent to 22 g ethanol. ††Trend for never and current drinkers. OR, odds ratio; CI, confidence interval.

Table 3 Odds ratios for bladder cancer by food consumption

Food	No. cases/controls Consumption level (lowest = 1)				OR (95% CI)† Consumption level (lowest = 1)				*P* for trend
	1	2	3	4	1	2	3	4	
Vegetables and fruit									
Fruit‡	51/192	22/151	51/276	–	1.00	0.64 (0.38–1.10)	0.85 (0.54–1.32)	–	0.50
Green vegetables§	20/77	56/228	35/197	13/116	1.00	1.05 (0.61–1.82)	0.79 (0.44–1.43)	0.57 (0.27–1.20)	0.063
Carrots§	33/158	57/245	28/127	6/88	1.00	1.13 (0.72–1.77)	1.15 (0.67–1.97)	0.41 (0.16–1.01)**	0.24
Pumpkin‡‡	26/93	50/249	35/181	13/94	1.00	0.77 (0.47–1.28)	0.80 (0.46–1.38)	0.62 (0.30–1.28)	0.26
Pickled Chinese cabbage‡‡	49/276	33/159	27/117	14/65	1.00	1.12 (0.70–1.79)	1.29 (0.78–2.14)	1.18 (0.62–2.23)	0.38
Vegetable pickles lightly preserved‡‡	24/156	25/150	40/176	34/135	1.00	1.06 (0.59–1.91)	1.32 (0.77–2.25)	1.46 (0.83–2.55)	0.13
Cabbage§	30/129	54/269	31/163	9/57	1.00	0.89 (0.55–1.43)	0.87 (0.51–1.49)	0.75 (0.34–1.65)	0.48
Lettuce‡‡	18/91	37/162	42/224	26/138	1.00	1.10 (0.61–2.00)	0.88 (0.49–1.60)	0.95 (0.51–1.80)	0.63
Meat, fish, and eggs									
Chicken‡‡	10/62	37/166	68/302	9/88	1.00	1.34 (0.64–2.78)	1.34 (0.67–2.68)	0.63 (0.25–1.59)	0.42
Beef‡‡	19/83	46/228	50/265	9/40	1.00	0.83 (0.47–1.47)	0.78 (0.44–1.36)	0.83 (0.36–1.93)	0.50
Pork‡‡	14/76	53/219	46/261	11/61	1.00	1.27 (0.68–2.38)	0.94 (0.50–1.78)	0.90 (0.39–2.07)	0.37
Ham and sausage‡‡	40/194	44/189	28/177	12/55	1.00	1.08 (0.69–1.71)	0.72 (0.43–1.20)	0.97 (0.49–1.94)	0.37
Dried/salted fish‡‡	22/100	37/222	45/225	18/70	1.00	0.71 (0.40–1.24)	0.85 (0.50–1.46)	1.05 (0.54–2.05)	0.70
Cooked/raw fish§	27/103	51/298	35/166	10/50	1.00	0.66 (0.40–1.10)	0.76 (0.44–1.31)	0.70 (0.32–1.54)	0.48
Eggs§	24/85	37/180	38/164	25/187	1.00	0.77 (0.45–1.34)	0.82 (0.48–1.42)	0.50 (0.27–0.90)*	0.030
Milk¶	35/156	42/193	37/198	10/69	1.00	0.99 (0.62–1.59)	0.95 (0.58–1.56)	0.71 (0.34–1.50)	0.47
Soybean products									
Soybean curds (tofu)§	20/80	50/268	39/161	14/107	1.00	0.75 (0.43–1.32)	0.96 (0.54–1.73)	0.57 (0.28–1.18)	0.38
Miso soup††	43/219	63/307	18/92		1.00	1.09 (0.72–1.64)	1.03 (0.58–1.83)	–	0.83

**$P < 0.10$, *$P < 0.05$. †Adjusted for age, sex, year of first visit and cumulative consumption of cigarettes. Subjects were categorized by intake frequency as follows: ‡Almost never or occasionally, 3–4 times/week and almost every day; §≤1–3 times/month, 1–2 times/week, 3–4 times/week, and ≥5 times/week; ‡‡Almost never, 1–3 times/month, 1–2 times/week, and ≥3–4 times/week; ¶Almost never, occasionally, 1 time/day, and ≥2 times/day; ††Almost never or occasionally, 1 time/day, and ≥2 times/day. OR, odds ratio; CI, confidence interval.

smokers. The risk for smokers compared with non-smokers did not vary substantially according to the consumption level of green–yellow vegetables. The OR were 1.85 (95% CI 0.90–3.82), 1.69 (95% CI 0.65–4.36) and 1.97 (95% CI 0.51–7.58) among those with low (intake score of 0.0–4.9), middle (5.0–9.9) and high (≥10.0) intake, respectively.

Multivariate analysis revealed that cigarette smoking and a moderate amount of green tea drinking were independently associated with an increased risk. In contrast, the frequent intake of green vegetables or eggs was related to a decreased risk (Table 5). If two or more factors coexist, the relative risk would theoretically be approximated by the product of corresponding OR. For example, those who have consumed 40–59 pack-years of cigarettes and drink green tea at a frequency of 5–9 cups/day may experience a 7.56-fold risk (= 2.71 × 2.79).

Consumption of black tea could not be incorporated in this multivariate analysis because only one case patient reported higher intake (≥1 cup/day). A strong correlation (Spearman's rank correlation coefficient = 0.59) between the consumption of green vegetables and carrots precluded simultaneous inclusion of the two vegetables in one logistic model. When carrots instead of green vegetables were included in the

Table 4 Odds ratios for bladder cancer by consumption of selected food groups

Food group	No. of cases/controls Intake score			OR (95% CI)† Intake score			*P* for trend
	0.0–4.9	5.0–9.9	≥10.0	0.0–4.9	5.0–9.9	≥10.0	
Green-yellow vegetables‡	72/299	38/188	14/131	1.00	0.92 (0.60–1.40)	0.54 (0.29–0.99)*	0.067
Other vegetables§	43/252	59/269	22/97	1.00	1.22 (0.81–1.86)	1.25 (0.73–2.14)	0.34
Meat¶	80/339	40/244	4/35	1.00	0.69 (0.46–1.03)**	0.42 (0.15–1.20)	0.023

**$P < 0.10$, *$P < 0.05$. †Adjusted for age, sex, year of first visit and cumulative consumption of cigarettes. ‡Green vegetables, carrots and pumpkin. §Pickled Chinese cabbage, vegetable pickles lightly preserved, cabbage and lettuce. ¶Chicken, beef, pork, and ham and sausage. OR, odds ratio; CI, confidence interval.

Table 5 Risk or protective factors for bladder cancer: multivariate analysis

Factor	OR†	95% CI
Cumulative consumption of cigarettes (pack-years)		
0	1.00	–
1–19	1.27	0.63–2.54
20–39	1.49	0.77–2.92
40–59	2.71	1.43–5.14**
≥60	2.37	1.18–4.77*
		P for trend = 0.002
Green tea intake (cups/day)		
<1	1.00	–
1–4	1.49	0.78–2.84
5–9	2.79	1.49–5.23**
≥10	1.24	0.51–2.99
		P for trend = 0.024
Intake frequency of green vegetables		
≤1–3 (times/month)	1.00	–
1–2 (times/week)	0.89	0.51–1.57
3–4 (times/week)	0.74	0.41–1.36
≥5 (times/week)	0.51	0.24–1.10‡
		P for trend = 0.060
Intake frequency of eggs		
≤1–3 (times/month)	1.00	–
1–2 (times/week)	0.72	0.41–1.27
3–4 (times/week)	0.78	0.45–1.38
≥5 (times/week)	0.54	0.30–0.99*
		P for trend = 0.078

†Adjusted for age, sex, year of first visit and all other variables listed in the table. ‡$P < 0.10$; *$P < 0.05$; **$P < 0.01$. CI, confidence interval; OR, odds ratio.

multivariate model, there also appeared a somewhat lower OR for the highest intake (≥5 times/week *vs* ≤1–3 times/month; OR 0.42, 95% CI 0.17–1.05; $P = 0.062$).

Discussion

The present study demonstrated a decreased risk of bladder cancer with frequent intake of green–yellow vegetables, which is in line with earlier findings.[2,11,26,27] Inverse associations were also suggested for black tea, egg and meat, whereas subjects who daily drank five to nine cups of green tea were at an enhanced risk. Consumption of coffee, milk or alcoholic beverages did not increase the risk.

Evidence for vegetable protection against bladder cancer is most abundant and consistent for green vegetables and carrots,[2] as corroborated here. If our results are applicable to the general population, a high intake of green–yellow vegetables (intake score ≥10.0) by all people could decrease the incidence of bladder cancer by 39.5%. Importantly, the OR for the highest intake of green–yellow vegetables was similarly low in both nonsmokers and smokers.

Although the protective effects of fruit have often been reported[2,11,27] and were supported by a meta-analysis,[28] we failed to find a significant reduction in risk. This may be because we covered fruit consumption with only one question and four possible responses instead of requesting separate and detailed information for several kinds of fruits. It may be difficult for subjects to appropriately answer highly combined or collapsed questions regarding fruit as a whole.[29] Furthermore, more categories for intake frequency may be required for appropriate assessment of fruit consumption.

We found no increase in risk with daily coffee consumption of three cups or more, consistent with the conclusion of a review[2] that coffee drinking is probably without influence at below five cups/day. A possible risk elevation at five cups/day or more could not be excluded because only a very small proportion of our controls (2.9%) drank coffee at such high levels.

The increased risk of bladder cancer in moderate drinkers of green tea (5–9 cups/day) is surprising given the postulated anticarcinogenic activities and protection afforded against various sites of cancer.[14] In addition, green tea dose-dependently inhibited the growth of urinary bladder tumors induced in rats by *N*-butyl-*N*-(4-hydroxybutyl) nitrosamine.[30] However, no relationship with risk was found in atomic-bomb survivors in Japan[11] and in men of Japanese ancestry in Hawaii.[4,15] Most green tea catechins, such as (–)-epigallocatechin gallate (EGCg), are absorbed in the form of degradation products produced by intestinal bacteria, then partly excreted in the urine, directly or after conjugation.[31] In epidemiological studies, interindividual differences in degradation activity may obscure any association of green tea consumption with bladder cancer risk. Furthermore, the individual antitumor activities of urinary EGCg metabolites have yet to be determined.[31]

We observed no dose–response relationship and could not consider total fluid intake[32] due to the limitations of the questionnaire. However, any association of risk with green tea drinking warrants further investigation because of potential mutagenicity of ingredients[33] and its popular use in Asian countries.[5]

According to a previous review[2] and a recent meta-analysis,[34] black tea probably neither increases nor decreases bladder cancer risk, although some epidemiological studies in Japan (Ohno *et al.*;[3] Wakai *et al.*, unpubl. data, 2000) have suggested a protective effect in line with our findings. Black tea drinking is not so popular in Japan,[3,11] so that the characteristics of drinkers may have confounded the results. In the present study, the decreased risk remained the same after adjustment for smoking and intake of green–yellow vegetables.

Although Riboli *et al.*[10] detected an increased risk of bladder cancer with a high consumption of milk and dairy products, one cohort[4] and four case-control studies[27,35–37] (including two conducted in Japan[27,37]) showed negative associations. Our results do not corroborate the potential protective effects, but add weight to the conclusion that dairy products are unlikely to increase the risk.

Several epidemiological studies have pointed to an increased risk of bladder cancer with meat intake,[6–8] but we have found a rather negative association, in line with the reported decreasing trend with meat consumption among women in the cohort study of Hirayama[9] in Japan. Another Japanese case-control study detected a non-significant inverse association[27] and a decreased risk in relation to chicken intake was found in a prospective study in Japan.[11] This discrepancy may be due, in part, to the far lower intake of meat in Japanese than in Western populations.[38] Differences in cooking methods may provide an alternative explanation. Balbi *et al.*[8] reported an elevated risk, particularly for salted and barbecued meat, which may be less frequently consumed in Japan.

The negative association demonstrated here for egg consumption may be a chance result because all previous studies reported no or positive associations.[2,8,11,27] Soybean curds (tofu) and miso soup are typical Japanese soybean products and rich in isoflavones,[12,13] but did

not decrease the risk significantly in this or earlier investigations.[4,11]

The role of fish in the etiology of urothelial cancer has not been studied considerably. However, in breast and colorectal cancer, possible protective effects of fish and its n-3 polyunsaturated fatty acids have been suggested and some mechanisms in the protection may be common also to other cancers.[39,40] The lower OR (0.66–0.76) for consumption of 1–2 times/week or more (*vs* ≤1–3 times/month) in Table 3, although not statistically significant, would be of interest in this context.

Some methodological limitations need consideration. First, we may have missed potential associations due to the relatively small number of cases ($n = 124$). We therefore included five controls/case. This resulted in a statistical power equivalent to that of a study with 207 cases and the same number of controls,[41] but the power may still have been insufficient and larger studies may have provided more meaningful information. Second, the possibility of selection bias arises because the controls were recruited from outpatients. However, we previously assessed the clinical diagnosis among randomly selected non-cancer outpatients to verify that 45% presented with no abnormal findings by examination and 35% with non-specific diseases.[16] Furthermore, evaluation of discrepant features of lifestyles between the outpatients and a random sample of the general population indicated that it is feasible to use such subjects as controls with due consideration of age, sex and season of survey.[42] Our controls were selected from cancer-free patients, matched for age and sex to each case. The seasonal distribution for questionnaire administration was also comparable between cases and controls.

In conclusion, men and women at an increased risk of bladder cancer, such as smokers, may benefit from increased consumption of green–yellow vegetables. Intervention trials in populations with extremely high risk (e.g. patients undergoing transurethral resection of bladder tumors, workers exposed to carcinogenic chemicals) are now warranted to confirm these protective effects.

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