25% lower benzo(a)pyrene (8.5 vs 11.4 ng/cig), 58% lower tobacco-specific nitrosamines (245 vs 580 ng/cig) and similar levels of nicotine.[1] Some disadvantages of the charcoal filter compared with typical acetate filters are increased gas phase concentration of the lung carcinogen isoprene, possibly increased production of reactive free radicals,[11] and manufacturing defects that contaminate the filter surfaces with charcoal granules.[12]

The delivery of tobacco smoke toxins from cigarettes with acetate filters tends to be greater under human smoking conditions than FTC machine-smoking conditions. These comparisons have not been conducted for charcoal cigarettes but suggest that the reduction in gas phase components associated with the charcoal filter might not be as high as under machine-smoking conditions. Within a single charcoal cigarette the levels of delivered toxins are much higher in the last puffs because the charcoal becomes inactive and deabsorbs gas phase compounds.[11] Consequently, the possible impact of charcoal filters on lung cancer risk might be affected by smoking behaviors such as number of puffs per cigarette and puff volume. Because the charcoal filter technology varies from brand to brand and is under continuous technological development,[13] the filtration efficiency, taste, aftertaste and possibly puffing habits might vary from one brand to another.

The current study did not find a reduced risk of lung cancer associated with charcoal filters. The strengths of our study included the high response rate in cases and hospital controls, a similar histologic distribution of lung cancer to that reported in a prospective study[14] and a similar percentage of subjects that smoked charcoal filter cigarettes as that reported in national sales data. The daily smoking amount increased slightly from the previous brand to the current brand, which is consistent with Japanese cigarette consumption statistics that show small annual increases in the average cpd.[15,16]

One limitation was that, as expected, the response rate among the community controls was lower than for hospital controls, although not atypical for elderly Japanese citizens contacted by telephone. The response rate of community controls in a study of colorectal cancer conducted in Fukuoka, Japan was 60%.[17] Although the response rate was somewhat lower here, we previously evaluated response bias for this community control group and reported few differences in years of smoking and cpd compared to population-based smoking surveys in Japan.[5] The current analysis also found few differences in the proportion of community versus hospital controls that smoked charcoal cigarettes. Self-reported smoking information such as cpd, years of smoking and year started is usually reported accurately. Still, there is little data on the reliability of self-reported information on brand name. One study found that the validity of self-reported cigarette brands was 74%.[18] In this study, the five most commonly reported brands corresponded to the rankings of Japanese national sales data (data not shown). Seventeen percent of subjects reported that the most recent cigarette smoked was a non-filter brand. This compares to 7.5% reported elsewhere.[9] However, our data included current and former smokers whereas Marugame *et al.* examined current smokers only.[9] The effects of residual confounding in smokers who switched from non-filter to filter cigarettes is another potential source of error. We excluded smokers whose two most recent brands were non-filter cigarettes but it was not possible to exclude subjects who smoked a non-filter during their early smoking years.

In summary, charcoal filter tips were not associated with a reduced lung cancer risk but this finding should be confirmed or refuted in further investigations because of their potential public health impact. The charcoal filter is one of several possible factors that might be associated with the lower smoking-associated risk of lung cancer in Japan. Other explanations include a lower baseline risk of lung cancer in Japanese non-smokers than in American smokers,[6] low saturated fat intake,[19] high fish consumption[20,21] and high green tea intake.[22] Green tea and other foods such as black tea and cruciferous vegetables inhibit cytochrome P4502E1 (CYP2E1) activity *in vitro* and in animals[23] and may contribute to the lower CYP2E1 activity in Japanese men than in Caucasian men.[24] Recent data also show that the 1960–1997 lung cancer incidence rates were similar between Japan and Japanese immigrants to Hawaii after several generations,[25] despite the lower prevalence of smoking in Japanese immigrants.[26,27] These data indicate that the Western diet may be important in explaining ethnic differences in lung cancer. There is no information on changes in the types of cigarettes preferred by Japanese immigrants to the US but this information would be useful in helping to explain these epidemiologic patterns.

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## References

1 Djordjevic MV, Eixarch L, Bush LP, Hoffmann D. A comparison of the yields of selected components in the mainstream smoke of the leading US and Japanese cigarettes. *Proceedings of the 1996 CORESTA Congress*; 6 Nov 1996, Yokahama Japan. 1996; 200–17.
2 Morrison CC, Wingate DE, Beard KA, Winkler LS, Simmons DF, Rogers JC, Borgerding MF. The effects of cigarette design modifications on selected mainstream vapor phase smoke constituent yields. *Proceedings of the 49th Tobacco Chemist Research Conference*; 24–27 Sep 1995. Lexington, KY, p. 44.
3 Wynder EL, Hirayama T. Comparative epidemiology of cancers of the United States and Japan. *Prev Med* 1977; **6**: 567–4.
4 Wynder EL, Fujita Y, Harris RE, Hirayama T, Hiyama T. Comparative epidemiology of cancer between the United States and Japan. A second look. *Cancer* 1991; **67**: 746–63.
5 Stellman SD, Takezaki T, Wang L, Chen Y, Citron ML, Djordjevic MV, Harlap S, Muscat JE, Neugut AI, Wynder EL, Ogawa H, Tajima K, Aoki K. Smoking and lung cancer risk in American and Japanese men: an international case-control study. *Cancer Epidemiol Biomarkers Prev* 2001; **10**: 1193–9.
6 Sobue T, Yamamoto S, Hara M, Sasazuki S, Sasaki S, Tsugane S, Study Group JPHC. Cigarette smoking and subsequent risk of lung cancer by histologic type in middle-aged Japanese men and women: the JPHC study. *Int J Cancer* 2002; **99**: 245–51.
7 Japanorama [website on the internet]. Japanese Cities Ranked by Population. 2001. [Cited Feb 2000.] Available from URL: http://www.japanorama.com/zip/cities_by_pop.pdf.
8 Thun MJ, Burns DM. Health impact of 'reduced yield' cigarettes: a critical assessment of the epidemiological evidence. *Tob Control* 2001; **10** (Suppl 1): 4–11.
9 Marugame T, Sobue T, Nakayama T, Suzuki T, Kuniyoshi H, Sunagawa K, Genka K, Nishizawa N, Natsukawa S, Kuwahara O, Tsubura E. Filter cigarette smoking and lung cancer risk: a hospital-based case-control study in Japan. *Br J Cancer* 2004; **90**: 646–51.
10 Hoffmann D, Djordjevic MV, Brunnemann K. Changes in cigarette design and composition over time and how they influence the yields of smoking constituents. *Natl Insts Health/Natl Cancer Inst Smoking Tobacco Control Monograph* 1996; **7**: 15–37.
11 Brunnemann KD, Kagan MR, Cox JE, Hoffmann D. Analysis of 1,3-butadiene and other selected gas-phase components in cigarette mainstream and sidestream smoke by gas chromatography-mass selective detection. *Carcinogenesis* 1990; **11**: 1863–8.
12 Pauly JL, Stegmeier SJ, Mayer AG, Lesses JD, Streck RJ. Release of carbon granules from cigarettes with charcoal filters. *Tob Control* 1997; **6**: 33–40.
13 Bombick DW, Bombick BR, Ayres PH, Putnam K, Avalos J, Borgerding MF, Doolittle DJ. Evaluation of the genotoxic and cytotoxic potential of mainstream whole smoke and smoke condensate from a cigarette containing a novel carbon filter. *Fundam Appl Toxicol* 1997; **39**: 11–17.
14 Yoshimi I, Ohshima A, Ajiki W, Tsukuma H, Sobue T. A comparison of trends in the incidence rate of lung cancer by histological type in the Osaka



 doi: 10.1111/j.1349-7006.2005.00045.x

Cancer Registry, Japan and in the Surveillance, Epidemiology and End Results Program, USA. *Jpn J Clin Oncol* 2003; **33**: 98–104.
15 Sato H, Araki S. Yields and daily consumption of cigarettes in Japan in 1969–96. *J Epidemiol* 2000; **10**: 7–15.
16 Yamaguchi N, Mochizuki-Kobayashi Y, Utsunomiya O. Quantitative relationship between cumulative cigarette consumption and lung cancer mortality in Japan. *Int J Epidemiol* 2002; **29**: 963–8.
17 Yin G, Kono S, Toyomura K, Hagiwara T, Nagano J, Mizoue T, Mibu R, Tanaka M, Kakeji Y, Maehara Y, Okamura T, Ikejiri K, Futami K, Yasunami Y, Maekawa T, Takenaka K, Ichimiya H, Imaizumi N. Methylenetetrahydrofolate reductase C677T and A1298C polymorphisms and colorectal cancer. The Fukuoka Colorectal Cancer Study. *Cancer Sci* 2004; **95**: 908–13.
18 Peach H, Shah D, Morris RW. Validity of smokers' information about present and past cigarette brands – implications for studies of the effects of falling tar yields of cigarettes on health. *Thorax* 1986; **41**: 203–7.
19 Wynder EL, Taioli E, Fujita Y. Ecologic study of lung cancer risk factors in the US and Japan, with special reference to smoking and diet. *Jpn J Cancer Res* 2002; **83**: 418–23.
20 Mulder I, Jansen MC, Smit HA, Jacobs DR Jr, Menotti A, Nissinen A, Fidanza F, Kromhout D. Role of smoking and diet in the cross-cultural variation in lung-cancer mortality: the Seven Countries Study. Seven Countries Study Research Group. *Int J Cancer* 2000; **88**: 665–71.
21 Nakaji S, Yoshioka Y, Mashiko T, Yamamoto Y, Kojima A, Baxter GD, Sugawara K. Explanations for the smoking paradox in Japan. *Eur J Epidemiol* 2003; **18**: 381–3.
22 Ji BT, Chow WH, Hsing AW, McLaughlin JK, Dai Q, Gao YT, Blot WJ, Fraumeni JF, Jr. Green tea consumption and the risk of pancreatic and colorectal cancers. *Int J Cancer* 1997; **70**: 255–8.
23 Kim RB, Yamazaki H, Chiba K, O'Shea D, Mimura M, Guengerich FP, Ishizaki T, Shimada T, Wilkinson GR. *In vivo* and *in vitro* characterization of CYP2E1 activity in Japanese and Caucasians. *J Pharmacol Exp Ther* 1996; **279**: 4–11.
24 Marchand LL, Wilkinson GR, Wilkens LR. Genetic and dietary predictors of CYP2E1 activity: a phenotyping study in Hawaii Japanese using chlorzoxazone. *Cancer Epidemiol Biomarkers Prev* 1999; **8**: 495–500.
25 Maskarinec G, Noh JJ. The effect of migration on cancer incidence among Japanese in Hawaii. *Ethn Dis* 2004; **14**: 431–9.
26 Health and Welfare Statistics Association. National trend of nutrition intake in Japan. *J Health Welfare Stat* 1996; **43**: 96–105. Special issue.
27 Ueshima H, Okayama A, Saitoh S, Nakagawa H, Rodriguez B, Sakata K, Okuda N, Choudhury SR, Curb JD, INTERLIPID Research Group. Differences in cardiovascular disease risk factors between Japanese in Japan and Japanese Americans in Hawaii: the INTERLIPID study. *J Hum Hypertens* 2003; **17**: 631–9.

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• *CLINICAL RESEARCH* •

# Development of a semi-quantitative food frequency questionnaire for middle-aged inhabitants in the Chaoshan area, China

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## Abstract

**AIM:** This paper aims to develop a data-based semi-quantitative food frequency questionnaire (SQFFQ) covering both urban and rural areas in the Chaoshan region of Guangdong Province, China, for the investigation of relationships between food intake and lifestyle-related diseases among middle-aged Chinese.

**METHODS:** We recruited 417 subjects from the general population and performed an assessment of the diet, using a 3-d weighed dietary record survey. We employed contribution analysis (CA) and multiple regression analysis (MRA) to select food items covering up to a 90% contribution and a 0.90 $R^2$, respectively. The total number of food items consumed was 523 (443 in the urban and 417 in the rural population) and the intake of 29 nutrients was calculated according to the actual consumption by foods/recipes.

**RESULTS:** The CA selected 233, 194, and 183 foods/recipes for the combined, the urban and the rural areas, respectively, and then 196, 157, and 160 were chosen by the MRA. Finally, 125 foods/recipes were selected for the final questionnaire. The frequencies were classified into eight categories and standard portion sizes were also calculated.

**CONCLUSION:** For adoption of the area-specific SQFFQ, validity and reproducibility tests are now planned to determine how the combined SQFFQ performs in actual assessment of disease risk and benefit.



**Key words:** Nutrients; Weighed diet records; Contribution analysis; Multiple regression analysis

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## INTRODUCTION

Lifestyle is the most important environmental factor related to chronic diseases such as cardiovascular diseases, diabetes and cancer[1-5], now the major causes of death in the developed countries and also increasing their impact in the developing world[6]. While genetic factors are also of interest in terms of etiology, from the viewpoint of disease prevention, environmental factors are more important, because they are controllable and thus targetable for health promotion. Unlike smoking, which only does harm to health[7], the diet has two profiles: appropriate intake is necessary for life, but excessive intake or imbalance may be deleterious. The investigation of reliable internal associations between food intake and health/diseases requires sufficient and accurate information on diet intake.

Increasing interest in relationships between long-term dietary intake and the occurrence of chronic disease has thus stimulated the development of evaluation methods to assess dietary factors among large groups of individuals. As a relatively new but efficient method, the semi-quantitative food frequency questionnaire (SQFFQ) has become widely used worldwide, especially in the US and European countries[8,9]. Compared with other approaches, the SQFFQ has the following advantages: (1) it is simple and convenient to implement; (2) it has the ability to provide food information over a relatively long time period; (3) it can be applied with focuses on specific age groups[10]. At present, the SQFFQ is therefore the best tool to obtain information for investigation of the relationship between the diet and health or disease.

Recently, the economic status in China has greatly improved, but a nationwide survey of food and nutrient intake in the country has revealed that geographical variations between urban and rural areas still exist in most regions. This variation demands the development of an appropriate SQFFQ covering both urban and rural populations to investigate the association between dietary factors and cancer risk, cases naturally being recruited from both areas. To develop a feasible combined SQFFQ, we here conducted a survey of food and nutrient intake using a 3-d weighed dietary record method (WDR) in urban and rural areas of Chaoshan.

## MATERIALS AND METHODS

The Chaoshan region, including Shantou, Chaozhou and Jieyang cities, is located in the east of Guangdong Province of China, with a population of approximately 10 million. People here still retain their own language and traditional culture. We have demonstrated that Nan'ao county in Chaoshan has the highest incidence and mortality rates of esophageal cancer in all China[11]. We here selected Chaozhou and Jieyang areas, including Nan'ao county, as representative of the countryside, and Shantou as representative of the new city.

### Study subjects

We initially recruited 520 healthy residents aged 30-55 years for participation in our investigation, but only 417 (200 males and 217 females) completed the 3-d WDR survey (70 in Chaozhou, 247 in Shantou and 100 in Nan'ao). The remainder dropped out because of their busy schedules or difficulties in recording. The fraction of sampling for the whole region was 41 per million.

Part juniors in the Chaozhou Normal College, staff of the Shantou Disease Preventive and Control Center, the Director General of the Nan'ao Board of Health and some doctors of Nan'ao Hospitals joined in our research team and were responsible for making contact with the subjects. Supervisors examined the completeness and accuracy of the information from the survey.

### Dietary assessment

A 3-d WDR (2 weekdays and 1 weekend day) was performed from December 2002 to August 2003, with a 24-h recall method also used as a supplement. Foods/recipes were individually weighed and recorded for their raw weights before cooking, except with cooked foods bought from markets. The completeness and accuracy of information were also reviewed by the research nutritionists.

### Nutrients of interest

The nutrients of interest comprised 29 items: energy, protein, fat, carbohydrates, crude fiber, retinol, carotene, vitamin C, vitamin E, folic acid, sodium, potassium, magnesium, calcium, iron, zinc, copper, selenium, phosphorus, saturated fatty acids (SFA), mono-unsaturated fatty acids (MUFA), poly-unsaturated fatty acids (PUFA), oleic acid, linoleic acid, arachidonic acid, linolenic acid, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and cholesterol.

### Selection of foods/recipes

Nutrient intake was calculated by multiplying the food intake (grams) by the nutrient content per gram of food listed in the China Food Composition 2002, compiled by the Institute of Nutrition and Food Safety, China CDC[12]. Where necessary we also used data from the Japanese Standard Tables of Food Composition, 5$^{th}$ revised edition[13] for the nutrient content of foods which were not listed in the China Food Composition.

The selection of food items for developing the SQFFQ was performed using the same procedure as adopted by Tokudome and his colleagues[14]. At first, contribution analysis (CA) was performed for all nutrients of interest[14-16], and each food item was listed according to the intake amount of nutrient. We selected food/recipe items with up to a 90% cumulative contribution. Then, multiple regression analysis (MRA) was carried out by adopting the total intake of specific nutrient as the dependent variable and overall amounts of this nutrient from the selected food/recipe items by CA as the independent variables for 417 individuals and secondly choosing foods/recipes with up to a 0.90 cumulative square of the multiple correlation coefficient[14,16]. Finally, we determined food items for the SQFFQ both by CA and MRA. Some food items with up to 0.90 $R^2$ but very small % contribution were excluded, because they may be marginal for total nutrient intake. The foods contributing less than three nutrients, with relatively small % contributions, were also excluded. The statistical package SPSS for Windows 10.0 (SPSS Inc., Chicago, IL, USA) was employed for the data analysis.

### Intake frequency

The food intake frequencies in SQFFQ were classified into seven categories: almost never; 1–3 times per month; 1-2 times per week; 3-4 times per week; 5-6 times per week; 1-2 times per day; and 3 times per day or more.

### Portion size

The standard portion size of each food item per meal was determined using the mean amount, typical/standard value or the natural unit. Portion size in SQFFQ was divided into six categories: none, 0.5, 0.75, 1.0, 1.5, 2.0 or more. As estimation of condiment and oil consumption per meal was difficult, four categories were employed: none, less than normal, normal and more than normal. The normal intake was determined as the mean amount in the 3-d WDR, and allocation to less or more than normal was estimated with reference to the standard deviation. We also took pictures of the most representative foods with a standard portion size and made a food model booklet for standardization of the intake amount.

## RESULTS

### Characteristics of the subjects studied

Table 1 shows the characteristics of the investigated subjects. The mean age was slightly older for the rural than the urban subjects in both genders. Although the mean height was not different, the mean weight and BMI in urban males were larger than those in their rural counterparts, with statistical significance. This was not the case for females.

### Intake of energy and selected nutrients

Table 2 shows mean intake and standard deviations for energy,

**Table 1** Characteristics of the investigated subjects

| | Males | | | Females | | |
|---|---|---|---|---|---|---|
| | Rural $n = 115$ | Urban $n = 102$ | *P* | Rural $n = 102$ | Urban $n = 98$ | *P* |
| Age (yr) | 43.1±6.9 | 42.4±7.1 | 0.803 | 42.9±6.8 | 41.3±7.7 | 0.245 |
| Height (cm) | 169.7±6.0 | 170.3±3.7 | 0.496 | 158.6±4.2 | 158.6±4.4 | 0.417 |
| Weight (kg) | 62.0±6.4 | 65.9±6.8 | 0.004 | 53.5±6.3 | 53.8±6.9 | 0.175 |
| BMI | 21.8±2.2 | 22.6±2.3 | 0.003 | 20.9±2.4 | 21.5±2.4 | 0.072 |

**Table 2** Intake of nutrients by the urban and rural subjects

| | Males | | | Females | | |
|---|---|---|---|---|---|---|
| | Rural $n = 115$ | Urban $n = 102$ | *P* | Rural $n = 102$ | Urban $n = 98$ | *P* |
| Energy (kcal) | 2 268±539 | 2 237±520 | 0.447 | 2 560±661 | 2 449±635 | 0.084 |
| Protein (g) | 83.5±26.7 | 85.5±23.8 | 0.375 | 85.0±27.4 | 91.8±27.3 | 0.244 |
| Fat (g) | 84.7±28.2 | 90.8±41.8 | 0.196 | 103.9±26.9 | 104.3±40.5 | 0.121 |
| Carbohydrate (g) | 295.1±106.8 | 271.9±101.1 | 0.320 | 327.2±129.8 | 301.3±111.8 | 0.758 |
| Crude fiber (g) | 10.2±4.7 | 10.0±3.7 | 0.707 | 9.5±3.6 | 12.0±9.8 | 0.017 |
| Cholesterol (mg) | 389.1±221.0 | 352.7±165.2 | 0.174 | 344.7±249.8 | 441.3±217.7 | 0.004 |
| Carotene (μg) | 2 576.7±2 105.7 | 2 693.8±2 009.1 | 0.675 | 2566.5±2132.6 | 3 487.0±1 872.2 | 0.001 |
| Retinol (μg) | 118.0±84.0 | 116.6±118.8 | 0.92 | 90.4±78.6 | 137.1±86.5 | 0.000 |
| Folic acid (mg) | 395.6±219.9 | 357.6±129.9 | 0.128 | 375.5±155.0 | 452.6±172.3 | 0.001 |
| Vitamin C (mg) | 88.4±52.3 | 80.4±39.6 | 0.205 | 96.2±61.0 | 102.2±38.8 | 0.416 |
| Vitamin E (mg) | 22.7±10.8 | 27.0±11.7 | 0.005 | 24.2±10.9 | 28.9±11.1 | 0.003 |
| Calcium (mg) | 525.6±191.7 | 446.8±190.2 | 0.412 | 406.9±187.4 | 505.0±155.1 | 0.000 |
| Phosphorus (mg) | 963.9±311.0 | 937.2±216.8 | 0.468 | 1 042.0±390.2 | 1 099.8±222.0 | 0.202 |
| Potassium (mg) | 1 718.0±575.5 | 1 745.0±459.3 | 0.705 | 1 808.9±666.6 | 2 006.6±453.2 | 0.015 |
| Sodium (mg) | 4 584.7±1 856.1 | 4 460.9±2 297.6 | 0.66 | 6 091.1±2 436.2 | 4 733.4±1 590.2 | 0.000 |
| Magnesium (mg) | 298.8±93.4 | 280.2±63.2 | 0.09 | 311.4±104.2 | 326.7±64.4 | 0.215 |
| Iron (mg) | 23.3± 8.8 | 22.9± 7.3 | 0.744 | 22.7±8.2 | 25.5±6.8 | 0.009 |
| Zinc (mg) | 12.73± 4.78 | 11.53±2.80 | 0.028 | 13.25±5.42 | 13.99±3.54 | 0.256 |
| Selenium (μg) | 64.92± 29.60 | 69.40±37.20 | 0.322 | 77.81±42.63 | 72.55±38.14 | 0.36 |
| Copper (mg) | 2.46±1.53 | 2.24±1.02 | 0.227 | 2.30±1.19 | 2.38±0.68 | 0.589 |
| SFA (g) | 21.14±7.51 | 22.83±7.92 | 0.107 | 24.12±10.56 | 25.84±8.78 | 0.215 |
| MUFA (g) | 32.05±10.68 | 35.83±10.47 | 0.009 | 36.53±15.36 | 42.34±10.26 | 0.002 |
| PUFA (g) | 18.62±8.27 | 23.01±9.70 | 0.000 | 21.90±15.58 | 26.41±8.92 | 0.013 |
| Oleic acid (g) | 29.40±9.79 | 33.12±9.76 | 0.005 | 33.50±13.74 | 38.46±9.39 | 0.003 |
| Linoleic acid (g) | 16.76±7.41 | 20.89±8.76 | 0.000 | 18.93±8.63 | 23.92±8.12 | 0.000 |
| Linolenic acid (g) | 1.64±1.30 | 1.67±1.46 | 0.895 | 1.74±1.62 | 2.76±2.06 | 0.000 |
| Arachidonic acid (g) | 0.088±0.041 | 0.087±0.041 | 0.951 | 0.092±0.056 | 0.096±0.047 | 0.626 |
| EPA (g) | 0.038±0.046 | 0.039±0.036 | 0.900 | 0.050±0.041 | 0.034±0.032 | 0.004 |
| DHA (g) | 0.079±0.100 | 0.069±0.063 | 0.385 | 0.118±0.095 | 0.072±0.073 | 0.000 |

SFA: saturated fatty acid; MUFA: mono-unsaturated fatty acid; PUFA: poly-unsaturated fatty acid; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid.

protein, fat, carbohydrate and other nutrients. Geographical variation of energy and major nutrient intake was not apparent in either sex, except for greater intake of crude fiber in urban males. Urban males and females consumed more vitamin E, MUFA, PUFA, oleic acid, and linoleic acid than rural subjects. In males, urban subjects consumed more cholesterol, carotene, retinol, folic acid, calcium, potassium and linolenic acid, whereas rural subjects had greater intakes of sodium, DHA and EPA. In females, rural subjects took more zinc and manganese.

We compared the consumption of each nutrient with the Recommended Nutrient Intake (RNI) for the first and second degree of work in China[17]. The energy consumption in our urban and rural males was similar to RNI, but with females the values were high. The consumption of protein and fat in both genders of urban and rural areas was higher than the RNI, especially for fat, but that for carbohydrate was relatively low.

### Selection of food items

The total number of food/recipe items consumed by all subjects over 3 d was 523 (443 and 417 in the urban and rural cases, respectively). The numbers of food items with up to 90% cumulative contribution for 29 nutrients were 233, 194, and 183 in the combined, urban and rural areas, and those for up to 0.9 cumulative $R^2$ were 196, 157, and 160, respectively. Then, we combined several food items with similar nutrient contents. Finally, we selected 125 food items for a combined SQFFQ. Alcohol beverages were not included in them, because the number of regular drinkers was very small. However, liquor and beer were intentionally added in this SQFFQ, because they are important dietary factors involved in the risk of diabetes and cancer[4,5].

The number of food items selected for each nutrient by CA and MRA are listed in Table 3. The mean numbers by CA were 58, 46, and 48 for the combined, the urban and

**Table 3** Numbers of foods contributing to 29 nutrients with up to 90 cumulative % and 0.9 cumulative $r^2$

| | Cumulative % | | | Cumulative $r^2$ | | |
|---|---|---|---|---|---|---|
| | Rural | Urban | Combined | Rural | Urban | Combined |
| Energy | 49 | 51 | 60 | 33 | 22 | 37 |
| Protein | 79 | 85 | 94 | 51 | 26 | 55 |
| Fat | 23 | 23 | 25 | 150 | 11 | 17 |
| Carbohydrate | 26 | 29 | 33 | 3 | 8 | 77 |
| Crude fiber | 65 | 61 | 74 | 74 | 13 | 21 |
| Cholesterol | 31 | 36 | 37 | 47 | 10 | 12 |
| Carotene | 23 | 21 | 38 | 47 | 12 | 8 |
| Retinol | 25 | 30 | 33 | 28 | 7 | 55 |
| Folic acid | 53 | 49 | 59 | 40 | 13 | 19 |
| Vitamin C | 38 | 27 | 44 | 52 | 17 | 70 |
| Vitamin E | 48 | 45 | 54 | 116 | 5 | 16 |
| Calcium | 94 | 93 | 104 | 70 | 19 | 30 |
| Phosphorus | 85 | 91 | 102 | 41 | 28 | 51 |
| Potassium | 114 | 99 | 120 | 63 | 36 | 1 |
| Sodium | 13 | 16 | 16 | 145 | 4 | 3 |
| Magnesium | 86 | 98 | 109 | 41 | 31 | 58 |
| Iron | 84 | 94 | 104 | 45 | 22 | 35 |
| Zinc | 72 | 78 | 86 | 41 | 15 | 44 |
| Selenium | 73 | 88 | 96 | 82 | 8 | 22 |
| Copper | 76 | 75 | 88 | 91 | 9 | 31 |
| SFA | 22 | 22 | 36 | 100 | 10 | 14 |
| MUFA | 16 | 17 | 21 | 70 | 9 | 8 |
| PUFA | 18 | 16 | 23 | 138 | 5 | 113 |
| Oleic acid | 15 | 15 | 17 | 142 | 6 | 8 |
| Linoleic acid | 17 | 15 | 18 | 143 | 5 | 8 |
| Linolenic acid | 31 | 28 | 56 | 136 | 1 | 2 |
| Arachidonic acid (g) | 24 | 32 | 53 | 53 | 17 | 17 |
| EPA | 22 | 32 | 51 | 30 | 17 | 23 |
| DHA | 14 | 29 | 36 | 24 | 13 | 12 |
| Mean | 46 | 48 | 58 | 72 | 14 | 30 |

SFA: saturated fatty acid; MUFA: mono-unsaturated fatty acid; PUFA: poly-unsaturated fatty acid; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid.

the rural cases, respectively, as compared with 30, 14, and 72 with the MRA.

### *List of food items*

The percentage contributions of the top five foods/recipes for energy, protein, fat and carbohydrate for rural, urban and combined areas are listed in Tables 4 and 5. Rice was the most important food source for energy, protein and carbohydrate intake, accounting for more than one-third of the energy, followed by peanut oil, pork, mixed oil, and lard, this being similar in both urban and rural areas. One-fourth of protein and more than two-thirds of carbohydrates

**Table 4** Percentage contributions of the top five foods for energy and protein

| Energy | | | | | | Protein | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Rural | | Urban | | Combined | | Rural | | Urban | | Combined | |
| Rice | 45.8 | Rice | 38.2 | Rice | 41.9 | Rice | 28.6 | Rice | 23.6 | Rice | 25.7 |
| Pork | 7.7 | Peanut oil | 8.9 | Peanut oil | 7.8 | Pork | 7.5 | Pork | 6.6 | Pork | 6.8 |
| Peanut oil | 6.9 | Pork | 6.9 | Pork | 7.1 | Grass carp | 3.4 | Beef | 4.0 | Grass carp | 3.6 |
| Mixed oil | 4.2 | Mixed oil | 6.4 | Mixed oil | 5.3 | Egg | 3.2 | Grass carp | 3.8 | Egg | 3.5 |
| Lard | 4.1 | Lard | 3.2 | Lard | 3.7 | Fish | 2.9 | Egg | 3.8 | Beef | 2.9 |

**Table 5** Percentage contribution of the top five foods for fat and carbohydrate

| Fat | | | | | | Carbohydrate | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Rural | | Urban | | Combined | | Rural | | Urban | | Combined | |
| Peanut oil | 21.7 | Peanut oil | 24.2 | Peanut oil | 22.9 | Rice | 70.4 | Rice | 67.5 | Rice | 70.4 |
| Pork | 20.2 | Mixed oil | 17.6 | Pork | 17.4 | Noodle | 3.2 | Noodle | 3.3 | Noodle | 3.2 |
| Mixed oil | 13.3 | Pork | 15.7 | Mixed oil | 15.6 | Bread | 2.3 | Bread | 3.0 | Bread | 2.3 |
| Lard | 13.1 | Lard | 11.0 | Lard | 11.0 | Rice noodles | 1.7 | Rice noodles | 2.1 | Rice noodles | 1.7 |
| Pork chops | 3.7 | Pork chops | 3.6 | Pork chops | 3.6 | White sugar | 1.6 | White sugar | 1.9 | White sugar | 1.6 |

were also contributed by rice. Peanut oil supplied more than one-fifth of fats, followed by pork, mixed oil, lard, pig chops and rice according to the CA. As for energy, the combined, urban and rural data also demonstrated almost have the same ranking for protein, fat and carbohydrate.

According to the category of the China Food Composition 2002, the 125 foods/recipes listed in the SQFFQ comprised: cereals (11 items), legumes (6), fresh legumes (3), vegetables (13), melons and nightshade (5), cauliflower (1), roots (7), fruits (11), meats (11), poultry (5), milk (2), eggs (3), pickles (4), marine products (16), mushrooms (5), nuts (2), cakes (3), condiments (6), oils (3) and beverages (8).

### *Nutrition coverage in the SQFFQ*

Table 6 shows the percentage coverage of 29 nutrients by the SQFFQ. The selected food items covered 17, 19, and 16 nutrients with up to 90% of the total intake for the rural, urban and combined SQFFQ, and the lowest coverage percentage of the combined SQFFQ was still 82.7%, for linolenic acid.

## DISCUSSION

The present study showed that variation in nutrient consumption between urban and rural subjects in the Chaoshan area was small, and the selected food items for the rural and urban SQFFQs were similar, covered all 29 nutrients with acceptable percentage values. The present results thus revealed that development of a combined SQFFQ for rural and urban populations is feasible.

The nationwide survey of China held in 1992 showed the national average energy intake to be higher in urban than in rural areas, especially in those with middle and high incomes[18]. Recent economic improvement may have reduced the variation in diet between rural and urban populations, and increased the amount of nutrient intake in both, but especially in rural individuals. The total energy intake in males was 2.4% higher in the present urban area and 21.0% higher in the rural area than those in the representative urban and rural areas of the same province by nationwide survey. The mean intakes of major nutrients in the present study were 6.4% higher in the urban area and 25.9% higher in the rural area for protein; 15.6% higher and 70.6% higher for fat; 2.1% lower and 1.0% higher for carbohydrate; and 31.9% higher and 15.9% higher for crude fiber, compared with the respective figures from the nationwide survey. The present urban population took more unsaturated fatty acid from vegetables, and the rural population took more animal fat, although geographical variation in total fat intake was not apparent.

Here we chose the 3-d WDR method as the "gold standard" rather than others to develop a SQFFQ for Chaoshan area, because it is the most efficient method for collecting dietary information at present. To decrease the

**Table 6** Percentage coverage of nutrients by the SQFFQ

| | % coverage | | |
|---|---|---|---|
| | Rural | Urban | Combined |
| Energy | 94.3 | 94.2 | 93.7 |
| Protein | 91.7 | 90.1 | 88.4 |
| Fat | 95.0 | 93.5 | 93.8 |
| Carbohydrate | 94.3 | 95.4 | 94.6 |
| Crude fiber | 86.5 | 87.3 | 87.5 |
| Cholesterol | 93.3 | 88.9 | 86.3 |
| Carotene | 88.7 | 93.9 | 90.3 |
| Retinol | 91.8 | 81.7 | 89.1 |
| Folic acid | 91.5 | 92.8 | 92.5 |
| Vitamin C | 86.3 | 94.6 | 91.2 |
| Vitamin E | 89.7 | 88.3 | 89.4 |
| Calcium | 87.3 | 87.3 | 88.6 |
| Phosphorus | 92.4 | 90.5 | 86.4 |
| Potassium | 86.8 | 90.5 | 88.2 |
| Sodium | 97.7 | 96.1 | 95.1 |
| Magnesium | 89.7 | 90.9 | 90.1 |
| Iron | 83.5 | 90.3 | 89.6 |
| Zinc | 90.9 | 91.9 | 91.6 |
| Selenium | 86.6 | 83.7 | 85.8 |
| Copper | 87.9 | 86.8 | 87.4 |
| SFA | 94.7 | 90.5 | 92.6 |
| MUFA | 96.2 | 95.6 | 88.4 |
| PUFA | 91.1 | 91.7 | 97.6 |
| Oleic acid | 96.5 | 95.7 | 90.2 |
| Linoleic acid | 94.2 | 92.1 | 97.6 |
| Linolenic acid | 91.2 | 92.2 | 82.7 |
| Arachidonic acid (g) | 90.3 | 88.5 | 92.7 |
| EPA | 82.4 | 80.2 | 87.6 |
| DHA | 88.4 | 81.9 | 82.9 |
| Mean | 90.7 | 90.2 | 90.0 |

SFA: saturated fatty acid; MUFA: mono-unsaturated fatty acid; PUFA: poly-unsaturated fatty acid; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid.

influence of seasonal variation on food survey, we conducted the survey in three seasons of winter, spring and summer, because there is no major climatic difference between the fall and winter. Although the sample size was relatively small, the number of subjects appeared sufficient from previous studies to develop SQFFQs, including the ones conducted in China[14,19,20].

We used the two contrasting methods of CA and MRA to select representative food items for stable food intake. Each method has its own particular advantages and disadvantages[13,14]. The former approach is based on the absolute food and nutrient intake and is especially suitable for investigation of the associations between absolute nutrient intake and disease risk. The latter, in contrast, is based on variance of nutrient intake, and is efficient for categorizing individuals. Therefore, the combination of the two methods for food selection should provide a more suitable SQFFQ for the assessment of food and nutrient intake.

We selected 125 food items, including alcoholic beverages, for the combined SQFFQ. Most were frequently consumed by the local inhabitants. Although the coverage rates of all 29 nutrients were over 80%, the potential for overestimation or underestimation does exist, because of the incompleteness of the composition table, and the exclusion of food items, such as some marine products, in the selection for the SQFFQ.

We have already developed data-based SQFFQs in Jiangsu, in the central coastal region of China, and Chongqing, more than 1 000 km west inland from Jiangsu, using a standardized method developed in Japan[14]. We compared the top three food items of three SQFFQs developed in Jiangsu[19], Chongqing[20] and the present study area, Chaoshan, more than 1 000 km south of Jiangsu, according to the percentage contribution for energy, protein, fat and carbohydrate by the urban and rural area (Table 7). Most items were shared in common, except for fat. These comparisons suggest the possibility to developing a common SQFFQ to assess and compare dietary factors impacting on cancer by the standardized method[21].

In summary, in the present investigation we clarified common intake of foods and 29 nutrients in urban and rural areas of Chaoshan, Guangdong Province, China, for adoption in an area-specific SQFFQ. Validity and reproducibility tests[22-24] are now planned to determine how the combined SQFFQ performs in the actual assessment of disease risk and benefit.

**Table 7** Comparison of percentage contributions of the top three foods for energy, protein, fat, and carbohydrates in urban and rural areas of Jiangsu, Chongqing and Chaoshan in China

| | Percentage contribution | | | | | |
|---|---|---|---|---|---|---|
| Energy | | | | | | |
| Urban | | | | | | |
| Jiangsu | Rice | 36.9 | Salad oil | 6.9 | Flour | 5.9 |
| Chongqing | Rice | 30.1 | Rape oil | 10.2 | Pork | 6.2 |
| Chaoshan | Rice | 45.8 | Pork | 7.7 | Peanut oil | 6.9 |
| Rural | | | | | | |
| Jiangsu | Rice | 39.5 | Lard | 14.2 | Pork | 5.3 |
| Chongqing | Rice | 32.1 | Rape oil | 12.2 | Flour | 7.7 |
| Chaoshan | Rice | 38.2 | Peanut oil | 8.9 | Pork | 6.9 |
| Protein | | | | | | |
| Urban | | | | | | |
| Jiangsu | Rice | 23.1 | Pork | 7.2 | Egg | 5.0 |
| Chongqing | Rice | 17.5 | Horse bean | 8.0 | Pork | 6.5 |
| Chaoshan | Rice | 28.6 | Pork | 7.5 | Grass card | 3.4 |
| Rural | | | | | | |
| Jiangsu | Rice | 34.4 | Pork | 6.5 | Egg | 4.3 |
| Chongqing | Rice | 20.4 | Pork | 7.4 | Flour | 7.0 |
| Chaoshan | Rice | 23.6 | Pork | 6.6 | Beef | 4.0 |
| Fat | | | | | | |
| Urban | | | | | | |
| Jiangsu | Salad oil | 22.1 | Soybean oil | 17.1 | Pork | 9.5 |
| Chongqing | Rape oil | 30.0 | Pork | 15.3 | Salad oil | 1.5 |
| Chaoshan | Peanut oil | 21.7 | Pork | 20.2 | Salad oil | 13.3 |
| Rural | | | | | | |
| Jiangsu | Lard | 45.8 | Pork | 16.4 | Rape oil | 11.7 |
| Chongqing | Rape oil | 32.3 | Lard | 13.5 | Pork | 12.2 |
| Chaoshan | Peanut oil | 24.2 | Salad oil | 17.6 | Pork | 15.7 |
| Carbohydrate | | | | | | |
| Urban | | | | | | |
| Jiangsu | Rice | 57.1 | Flour | 8.7 | Noodle | 2.9 |
| Chongqing | Rice | 55.1 | Flour | 10.3 | Noodle | 7.9 |
| Chaoshan | Rice | 73.7 | Noodle | 2.8 | Bread | 1.7 |
| Rural | | | | | | |
| Jiangsu | Rice | 59.6 | Noodle | 5.8 | Corn | 5.7 |
| Chongqing | Rice | 60.1 | Flour | 16.6 | Peas | 2.8 |
| Chaoshan | Rice | 67.5 | Noodle | 3.3 | Bread | 3.0 |

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## REFERENCES

1 **Chen H**, Zhang S, Hernan M, Willett WC, Ascherio A. Dietary intakes of fat and risk of Parkinson's disease. *Am J Epidemiol* 2003; **157**: 1007-1014

2 **Blumenfeld A**, Fleshner N, Casselman B, Trachtenberg J. Nutritional aspects of prostate cancer: a review. *Can J Urol* 2000; **7**: 927-935

3 **Swinburn B**. Sustaining dietary changes for preventing obesity and diabetes: lessons learned from the successes of other epidemic control programs. *Asia Pac J Clin Nutr* 2002; **11** (Suppl 3): S598-606

4 **Wannamethee S**, Camargo C Jr, Manson J. Alcohol drinking patterns and risk of type 2 diabetes mellitus among younger women. *Arch Intern Med* 2003; **163**: 1329-1336

5 **Willett W**. Diet and cancer. *Oncologist* 2000; **5**: 393-404

6 **Kopczynski J**, Wojtyniak B, Gorynski P, Lewandowski Z. The future of chronic diseases. *Cent Eur J Public Health* 2001; **9**: 3-13

7 **Pride N**, Soriano J. Chronic obstructive pulmonary disease in the United Kingdom: trends in mortality, morbidity, and smoking. *Curr Opin Pulm Med* 2002; **8**: 95-101

8 **Bergmann M**, Bussas U, Boeing H. Follow-up procedures in EPIC-Germany-data quality aspects. European prospective investigation into cancer and nutrition. *Ann Nutr Metab* 1999; **43**: 225-234

9 **Key TJ**, Appleby PN, Davey GK, Allen NE, Spencer EA, Travis RC. Mortality in British vegetarians: review and preliminary results from EPIC-Oxford. *Am J Clin Nutr* 2003; **78** (3 Suppl): 533S-538

10 **Willett W**, Colditz G. Approaches for conducting large cohort studies. *Epidemiol Rev* 1998; **20**: 91-99

11 **Li K**. Mortality and incidence trends from esophagus cancer in selected geographic areas of China circa 1970-90. *Int J Cancer* 2002; **102**: 271-274

12 **Yang YX**, Wang GY, Pan XC. China Food Composition 2002. Beijing: *Peking University Medical Press* 2002: 21-338

13 Resources Council, Science and Technology Agency, Japan. Standard Tables of Food Composition in Japan, 5th revised ed. Tokyo: *Resource Council Science and Technology Agency* 2000: 29-303

14 **Tokudome S**, Ikeda M, Tocudome Y, Imaeda N, Kitagawa I, Fujiwara N. Development of a data-based semi-quantitative food Frequency questionnaire for dietary studies in middle-aged Japanese. *Jpn J Clin Oncol* 1998; **28**: 679-687

15 **Stiggelbout AM**, van der Giezen AM, Blauw YH, Blok E, van Staveren WA, West CE. Development and relative validity of a food frequency questionnaire for the estimation of intake of retinol and beta-carotene. *Nutr Cancer* 1989; **12**: 289-299

16 **Overvad K**, Tjonneland A, Haraldsdottir J, Ewertz M, Jensen OM. Development of a semiquantitative food frequency questionnaire to assess food, energy and nutrient intake in Denmark. *Int J Epidemiol* 1991; **20**: 900-905

17 Chinese Nutrition Society. Chinese Dietary Reference Intakes, DRIs. *Yingyang Xuebao* 2001; **3**: 193-196

18 **Ge KY**, Zhai FY, Yan HC, Cheng L, Wang Q, Jia FM. The dietary and nutritional status of chinese population in 1990s. *Yingyang Xuebao* 1995; **2**: 123-134

19 **Wang YM**, Mo BQ, Takezaki T, Imaeda N, Kimura M, Wang XR, Tajima K. Geographical variation in nutrient intake between urban and rural areas of Jiangsu province, China and development of a semi-quantitative food frequency questionnaire for middle-aged inhabitants. *J Epidemiol* 2003; **13**: 80-89

20 **Zhou Z**, Takezaki T, Mo B, Sun H, Wang W, Sun L, Liu S, Ao L, Cheng G, Wang Y, Cao J, Tajima K. Geographical variation in nutrient intake between urban and rural areas of Chongqing, China and development of a data-based semi-quantitative food frequency questionnaire for both populations. *Asia Pac J Clin Nutr* 2004; **13**: 273-283

21 **Aydemir G**. Research on nutrition and cancer: The importance of the standardized dietary assessments. *Asian Pac J Cancer Prev* 2002; **3**: 177-180

22 **Tokudome S**, Imaeda N, Tocudome Y, Fujiwara N, Nagaya T, Sato J, Kuriki K, Ikeda M, Maki S. Relative validity of a semi-quantitative food frequency questionnaire versus 28 d weighed diet records in Japanese female dietitians. *Eur J Nutr* 2001; **55**: 735-742

23 **Imaeda N**, Fujiwara N, Tokudome Y, Ikeda M, Kuriki K, Nagaya T, Sato J, Goto C, Maki S, Tokudome S. Reproducibility of a semi-quantitative food frequency questionnaire in Japanese female dietitians. *J Epidemiol* 2003; **12**: 45-53

24 **Kim J**, Kim DH, Ahn YO, Tokudome Y, Hamajima N, Inoue M, Tajima K. Reproducibility of a food frequency questionnaire in Koreans. *Asian Pac J Cancer Prev* 2003; **4**: 253-257

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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 *n* | Cases % | Controls *n* | Controls % | OR† | 95% CI |
|---|---|---|---|---|---|---|
| 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 nonsmokers 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 non-smokers 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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## References


1 Coleman MP, Esteve J, Damiecki P, Arslan A, Renard H. *Trends in Cancer Incidence and Mortality.* IARC, Lyon, 1993.

2 World Cancer Research Fund, American Institute for Cancer Research. Cancers, nutrition and food: Bladder. In: *Food, Nutrition and the Prevention of Cancer: A Global Perspective.* American Institute for Cancer Research, Washington, 1997; 338–61.

3 Ohno Y, Aoki K, Obata K, Morrison AS. Case-control study of urinary bladder cancer in metropolitan Nagoya. *Natl Cancer Inst. Monogr.* 1985; **69**: 229–34.

4 Chyou PH, Nomura AMY, Stemmermann GN. A prospective study of diet, smoking, and lower urinary tract cancer. *Ann. Epidemiol.* 1993; **3**: 211–16.

5 Lu CM, Lan SJ, Lee YH, Huang JK, Huang CH, Hsieh CC. Tea consumption: Fluid intake and bladder cancer risk in Southern Taiwan. *Urology* 1999; **54**: 823–8.

6 Steineck G, Norell SE, Feychting M. Diet, tobacco and urothelial cancer. A 14-year follow-up of 16 477 subjects. *Acta Oncol.* 1988; **27**: 323–7.

7 Fraser GE. Associations between diet and cancer, ischemic heart disease, and all-cause mortality in non-Hispanic white California Seventh-day Adventists. *Am. J. Clin. Nutr.* 1999; **70** (Suppl): 532–8.

8 Balbi JC, Larrinaga MT, De Stefani E *et al.* Foods and risk of bladder cancer: A case-control study in Uruguay. *Eur. J. Cancer Prev.* 2001; **10**: 453–8.

9 Hirayama T. *Life-Style and Mortality: A Large-Scale Census-Based Cohort Study in Japan.* Karger, Basel, 1990.

10 Riboli E, Gonzalez CA, Lopez-Abente G *et al.* Diet and bladder cancer in Spain: A multi-centre case-control study. *Int. J. Cancer* 1991; **49**: 214–19.

11 Nagano J, Kono S, Preston DL *et al.* Bladder-cancer incidence in relation to vegetable and fruit consumption: A prospective study of atomic-bomb survivors. *Int. J. Cancer* 2000; **86**: 132–8.

12 Kimira M, Arai Y, Shimoi K, Watanabe S. Japanese intake of flavonoids and isoflavonoids from foods. *J. Epidemiol.* 1998; **8**: 168–75.

13 Wakai K, Egami I, Kato K *et al.* Dietary intake and sources of isoflavones among Japanese. *Nutr. Cancer* 1999; **33**: 139–45.

14 Mukhtar H, Ahmad N. Tea polyphenols: Prevention of cancer and optimizing health. *Am. J. Clin. Nutr.* 2000; **71** (Suppl): 1698–702.

15 Wilkens LR, Kadir MM, Kolonel LN, Nomura AMY, Hankin JH. Risk factors for lower urinary tract cancer: The role of total fluid consumption, nitrites and nitrosamines, and selected foods. *Cancer Epidemiol. Biomarkers Prev.* 1996; **5**: 161–6.

16 Inoue M, Tajima K, Hirose K *et al.* Subsite-specific risk factors for colorectal cancer: A hospital-based case-control study in Japan. *Cancer Causes Control* 1995; **6**: 14–22.

17 Tajima K, Hirose K, Inoue M, Takezaki T, Hamajima N, Kuroishi T. A model of practical cancer prevention for out-patients visiting a hospital: The Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC). *Asian Pacific J. Cancer Prev.* 2000; **1**: 35–47.
18 World Health Organization. *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*, **Vol. 1**. World Health Organization, Geneva, 1992.
19 Japanese Urological Association, The Japanese Pathological Society. *General Rule for Clinical and Pathological Studies on Bladder Cancer*, 1st edn. Kanehara, Tokyo, 1980.
20 Japanese Urological Association, The Japanese Society of Pathology. *General Rule for Clinical and Pathological Studies on Renal, Pelvic and Ureteral Cancer*, 1st edn. Kanehara, Tokyo 1990.
21 Breslow NE, Day NE. Conditional logistic regression for matched sets. In: Davis W (eds). *Statistical Methods in Cancer Research*, **Vol. 1**. IARC, Lyon, 1980; 248–79.
22 Breslow NE, Day NE. Unconditional logistic regression for large strata. In: Davis W (eds). *Statistical Methods in Cancer Research*, **Vol. 1**. IARC, Lyon, 1980; 192–246.
23 Bruemmer B, White E, Vaughan TL, Cheney CL. Nutrient intake in relation to bladder cancer among middle-aged men and women. *Am. J. Epidemiol.* 1996; **144**: 485–95.
24 Miettinen OS. Proportion of disease caused or prevented by a given exposure, trait or intervention. *Am. J. Epidemiol.* 1974; **99**: 325–32.
25 SAS Institute Inc. *SAS/STAT User's Guide, Version 8*. SAS Institute Inc., Cary, 1999.
26 Pohlabeln H, Jöckel KH, Bolm-Audorff U. Non-occupational risk factors for cancer of the lower urinary tract in Germany. *Eur. J. Epidemiol.* 1999; **15**: 411–19.
27 Wakai K, Takashi M, Okamura K *et al.* Foods and nutrients in relation to bladder cancer risk: A case-control study in Aichi Prefecture, Central Japan. *Nutr. Cancer* 2000; **38**: 13–22.
28 Steinmaus CM, Nuñez S, Smith AH. Diet and bladder cancer: A meta-analysis of six dietary variables. *Am. J. Epidemiol.* 2000; **151**: 693–702.
29 Willett W. Food-frequency methods. In: Willett W (ed.). *Nutritional Epidemiology*, 2nd edn. Oxford University Press, Oxford, 1998; 74–100.
30 Sato D. Inhibition of urinary bladder tumors induced by *N*-butyl-*N*-(4-hydroxybutyl)-nitrosamine in rats by green tea. *Int. J. Urol.* 1999; **6**: 93–9.
31 Kohri T, Matsumoto N, Yamakawa M *et al.* Metabolic fate of (–)-[4-$^3$H]epigallocatechin gallate in rats after oral administration. *J. Agric. Food Chem.* 2001; **49**: 4102–12.
32 Geoffroy-Perez B, Cordier S. Fluid consumption and the risk of bladder cancer: Results of a multicenter case-control study. *Int. J. Cancer* 2001; **93**: 880–7.
33 Tewes FJ, Koo LC, Meisgen TJ, Rylander R. Lung cancer risk and mutagenicity of tea. *Environ. Res.* 1990; **52**: 23–33.
34 Zeegers MPA, Tan FES, Goldbohm RA, van den Brandt PA. Are coffee and tea consumption associated with urinary tract cancer risk? A systematic review and meta-analysis. *Int. J. Epidemiol.* 2001; **30**: 353–62.
35 Mettlin C, Graham S. Dietary risk factors in human bladder cancer. *Am. J. Epidemiol.* 1979; **110**: 255–63.
36 Slattery ML, West DW, Robison LM. Fluid intake and bladder cancer in Utah. *Int. J. Cancer* 1988; **42**: 17–22.
37 Nakata S, Sato J, Ohtake N, Imai K, Yamanaka H. Epidemiological study of risk factors for bladder cancer. *Acta Urol. Jpn.* 1995; **41**: 969–77.
38 Food and Agriculture Organization. Food and Agriculture Organization database [Internet]. Rome: Food and Agriculture Organization; [cited 2 June, 2003]. Available from: http://apps.fao.org/)
39 Bartsch H, Nair J, Owen RW. Dietary polyunsaturated fatty acids and cancers of the breast and colorectum: Emerging evidence for their role as risk modifiers. *Carcinogenesis* 1999; **20**: 2209–18.
40 de Deckere EA. Possible beneficial effect of fish and fish n-3 polyunsaturated fatty acids in breast and colorectal cancer. *Eur. J. Cancer Prev.* 1999; **8**: 213–21.
41 Breslow NE, Day NE. Design considerations. In: Heseltine E (ed.). *Statistical Methods in Cancer Research*, **Vol. 2**. IARC, Lyon, 1987; 271–314.
42 Inoue M, Tajima K, Hirose K *et al.* Epidemiological features of first-visit outpatients in Japan: Comparison with general population and variation by sex, age, and season. *J. Clin. Epidemiol.* 1997; **50**: 69–77.