Dietary factors and lung cancer risk in Japanese: with special reference to fish consumption and adenocarcinomas

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Summary To investigate risk modification for lung cancer with diet in Japanese, we conducted a hospital-based case–control study and evaluated variation in influence with the histological type. We recruited 367 male and 240 female cases with adenocarcinomas, and 381 male and 57 female cases with squamous cell and small cell carcinomas. Controls comprised 2964 male and 1189 female cancer-free outpatients matched for sex and age with the cases. Odds ratios (ORs) and their 95% confidence intervals (CIs) for lung cancer were calculated with adjustment for potential confounding factors, using an unconditional logistic model. We found decreased ORs for adenocarcinomas in both males (OR = 0.51, 95% CI 0.31–0.84) and females (OR = 0.48, 95% CI 0.24–0.94) who consumed cooked/raw fish, but not dried/salted fish at the highest quartile frequency, compared with the lowest. Soybean curd consumption was associated with a decreased OR for female adenocarcinomas. Decreased ORs for squamous cell and small cell carcinomas were observed in males with frequent consumption of raw and green vegetables, fruit and milk, but consumption of carrot, pumpkin, egg and coffee was associated with increased ORs. This study suggests cooked/raw fish consumption lowers the risk of adenocarcinoma of the lung in Japanese. © 2001 Cancer Research Campaign http://www.bjcancer.com

Keywords: fish consumption; lung neoplasms; risk; adenocarcinoma

Lung cancer is the leading cause of death among malignancies in Japan (Statistics and Information Department, Ministry of Health and Welfare, 2000). Its age-adjusted mortality and incidence rates, however, are still less than two-thirds of those in the US and the UK (Parkin et al, 1999; Pisani et al, 1999). Wynder and Hoffmann have pointed out the importance of dietary factors as underlying reasons for the lower lung cancer death rates observed in Japan, in addition to age at onset of cigarette smoking, personal smoking behaviour and the make-up of cigarettes (Wynder and Hoffmann, 1994). Japanese specific dietary factors that may protect against cancer development include frequent consumption of soybean products, green tea and fish. We here examine the hypothesis that intake of these foods modifies the risk of lung cancer in Japanese.

A number of studies have revealed negative associations between fish consumption and lung cancer risk (Koo, 1988; Pierce et al, 1989; Veierod et al, 1997). Furthermore, an inverse correlation between fish consumption and male lung cancer mortality was observed in a recent international ecological study (Zhang et al, 2000). However, a protective effect of fish consumption with regard to lung cancer risk is not yet conclusive (World Cancer Research Fund, 1997), and one problem is the variety of forms of lung neoplasia. We are aware of no published reports focused on the risk for lung cancer with fish consumption by histological type. N-3 polyunsaturated fatty acids (PUFA) present in fish oil, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), exert inhibitory effects on development of human lung mucoepidermoid

and other carcinomas (Karmali et al, 1984; de Bravo et al, 1991; Ling et al, 1991; Rose and Connoclly, 1991; Singh et al, 1997).

Experimental studies have revealed protective effects of isoflavones from soybeans and epigallocatechin gallate from green tea against lung cancer development (Kinlen et al, 1988; Messina et al, 1994; Fujiki et al, 1998; Lian et al, 1999). Several studies in Japan and China have shown risk reduction of lung cancer with consumption of soybean products (Koo, 1988; Wakai et al, 1999a) and green tea (Kinlen et al, 1988; Ohno et al, 1995), but again data for histological types are limited.

To investigate the association between food consumption and lung cancer risk with reference to histopathological diagnosis, we here conducted a hospital-based case–control study.

SUBJECTS AND METHODS

Study subjects and data collection

Since 1988, a self-administered questionnaire has been completed by first-visit outpatients before undergoing medical examinations at Aichi Cancer Center Hospital in Nagoya, Japan (Hospital-Based Epidemiologic Research Program at Aichi Cancer Center: HERPACC). Details of the questionnaire and data collection procedures have been described elsewhere (Inoue et al, 1995; Tajima et al, 2000). In brief, an expert interviewer checks all written responses at the time of collection within the first-visit day. Included are questions on demographic information, prior medical history, family history, smoking and drinking habits, general health condition, reproduction, and food intake before the onset of the current symptoms. Questions regarding green tea and coffee consumption were added in 1990. The data are annually linked to the hospital cancer-registry system to obtain information on

confirmed diagnosis one year after the first visit. Between 1988 and 1997, questionnaires were handed out to 67 854 (91.3%) first-visit outpatients ($n = 74 280$), and collected with a high response rate (98.6%).

From 1988 to 1997, 1474 cases presented at the Hospital Departments of Internal Medicine or Thoracic Surgery, Aichi Cancer Center Hospital, as first-visit outpatients, and were histologically diagnosed as having primary cancer of the lung (ICD9-162 or ICD10-C34). The histological classification was performed according to the criteria of the World Health Organization (World Health Organization, 1981). Operations were performed in 658 cases, and the diagnosis in the remaining 816 cases was confirmed by biopsy and cytological examination. Of the total, 1212 cases answered our questionnaire. The remaining 263 were hospitalized without taking outpatient service, or were unable to answer the questions because of severe symptoms. The patients with large cell carcinomas of the lung were not included in the cases, because their number (67 males and 11 females) was not sufficient for analyses. We also excluded patients who had missing values for smoking status or fish consumption. Finally, 748 male and 297 female patients aged 40 to 79 years who were histologically diagnosed as having adenocarcinomas, squamous cell carcinomas, or small cell carcinomas of the lung were eligible as study subjects.

The controls were outpatients confirmed to be cancer-free by diagnostic procedures at Aichi Cancer Center Hospital between 1988 and 1997. Also excluded were those with a prior medical history of cancer, with unrecorded smoking status or fish consumption details, or who had been referred from doctors, a group with a high potential for having precancerous diseases. Of the remaining 10 418 male and 23 841 female outpatients, we, then, randomly selected 4 controls per one case after matching sex and age (within 5 years). Finally, 2964 males and 1189 females were eligible for the control group.

Data analysis

We defined current smokers as persons who had smoked for one year or more, or had quit smoking less than one year before the questionnaire study, ex-smokers as those who had smoked for one year or more and quit smoking one year or more before the study, and never-smokers as those who never smoked or smoked for less than one year. We similarly divided smoking status of husbands into 3 categories as never smokers, former smokers, and current smokers. Females with no husband were included in the category of never smokers for smoking status of husband. We categorized current and prior occupations into 2 groups, blue-collar workers, and white-collar workers, because previous studies reported a positive association between the former and risk for lung cancer (Blot and Fraumeni, 1996). Medical staffs were included as blue-collar workers and housewives as white-collar workers. With regard to personal history, prior lung diseases taken into account included bronchitis, pneumonia, pleurisy, lung abscess formation, pneumothorax, interstitial pneumonia, and chronic obstructive lung diseases.

3 dietary habits, 2 beverages and 24 food items were analysed as factors. Beverages and food items were divided into 4 or 5 groups according to frequency of consumption before the onset of the current symptoms. These groups were further divided into quartile subgroups, each comprising approximately 25% of the controls. Cooked/raw fish was considered separately from dried/salted fish.

We combined cases with squamous cell carcinoma and small cell carcinoma, because the small number of male nonsmoking cases (1 patient with squamous cell carcinoma and 2 patients with small cell carcinoma) led to an unstable estimation of odds ratios (ORs) and their 95% confidence intervals (CIs).

Statistical analysis

For data analyses, ORs and their 95% CIs of all items for cases and controls were calculated, using the unconditional logistic regression model (Breslow and Day, 1980). P values for trend in the OR were calculated by the chi-square test in the unconditional logistic regression model after making dummy variables, such as 0, 1, 2 and 3. To control for the effects of potential confounding factors, ORs were calculated after adjustment for age (continuous), year and season of the questionnaire study, occupation, smoking status (never, former, current (<20 cigarettes/day) or current (≥20 cigarettes/day)), passive smoking exposure from husbands (never or no husband, former, or current), prior lung diseases, and consumption of green vegetables and meat. The procedure LOGISTIC from the statistical package SAS, version 6.12 (SAS Institute, Cary, NC) was used for the calculations.

RESULTS

The age distributions of total cases and controls were quite similar, but the average age of adenocarcinoma cases was younger and that of squamous cell and small cell carcinoma cases was older than for the controls (Table 1A, 1B). Current smoking was associated with increased ORs for male and female squamous cell and small cell carcinomas, and male adenocarcinomas, being especially pronounced with squamous cell and small cell carcinomas and heavy smokers (≥20 cigarettes/day). Increased ORs for adenocarcinomas were found for both male and female blue-collar workers. A personal history of prior lung disease was related to increased ORs for adenocarcinomas, as well as squamous cell and small cell carcinomas in both males and females.

In males, we found a decreased OR (0.51; 95% CI = 0.31–0.84) for adenocarcinomas with the highest quartile consumption of cooked/raw fish, compared with the lowest (Table 2A), the decreasing trend being statistically significant ($P = 0.039$). The ORs for squamous cell and small cell carcinomas for fish consumption also showed a tendency for decrease but without statistical significance ($P = 0.112$). Dried/salted fish consumption was not associated with decreased ORs for adenocarcinomas, or squamous cell and small cell carcinomas. Consumption of raw and green vegetables, fruit and milk revealed a significant decreasing trend of ORs for squamous cell and small cell carcinomas, and a decreasing trend of ORs for adenocarcinomas was observed in cases with frequent consumption of green vegetables. In contrast, consumption of carrot, pumpkin, egg and coffee was associated with increased ORs for squamous cell and small cell carcinomas, with statistical significance. Frequent consumption of miso soup increased the ORs for squamous cell and small cell carcinomas, without statistical significance for the trend ($P = 0.112$). Frequent consumption of pickles of Chinese cabbages also tended to be associated with increased OR for squamous cell and small cell carcinomas.

In females, the highest quartile consumption of cooked/raw fish also decreased the OR (0.48; 95% CI = 0.24–0.94) for adenocarcinomas, but not for squamous cell and small cell carcinomas

Table 1A Comparison of baseline lung cancer risk factors by histological type in males, Aichi Cancer Center Hospital, 1988–97

| | Referents | Cases | | | | | |
| | | Adenocarcinomas | | | Squamous cell & small cell carcinomas | | |
	No.	No.	OR[a]	(95% CI)	No.	OR[a]	(95% CI)
Age in years							
40–49	288	54			18		
50–59	856	121			93		
60–69	1099	117			157		
70–79	721	75			113		
Total	2964	367			381		
Average age in years	62.1	60.2			64.2		
Smoking status							
Never	632	35	1.00	–	3	1.00	–
Former	1100	86	1.52	(1.00–2.29)	88	15.5	(4.87–49.3)
Current	1232	246	3.71	(2.56–5.37)	290	52.4	(16.7–164)
<20 cigarrettes/day	399	48	2.25	(1.42–3.55)	53	25.6	(7.93–82.6)
≥20 cigarrettes/day	826	198	4.38	(3.00–6.40)	235	70.0	(22.3–220)
Occupation							
White-collar workers	2175	239	1.00	–	287	1.00	–
Blue-collar workers	789	128	1.46	(1.16–1.85)	94	0.91	(0.71–1.17)
Prior lung diseases							
No	2845	342	1.00	–	342	1.00	–
Yes	119	25	1.81	(1.15–2.84)	39	2.65	(1.81–3.89)

[a]Adjusted for age (continuous), and year and season of questionnaire study.

Table 1B Comparison of baseline lung cancer risk factors by histological type in females, Aichi Cancer Center Hospital, 1988–97

| | Referents | Cases | | | | | |
| | | Adenocarcinomas | | | Squamous cell & small cell carcinomas | | |
	No.	No.	OR[a]	(95% CI)	No.	OR[a]	(95% CI)
Age in years							
40–49	220	46			9		
50–59	352	76			12		
60–69	416	81			23		
70–79	201	37			13		
Total	1189	240			57		
Average age in years	59.5	59.0			61.6		
Smoking status							
Never	1043	209	1.00	–	20	1.00	–
Former	45	8	0.89	(0.41–1.93)	5	6.33	(2.14–18.7)
Current	101	23	1.13	(0.70–1.84)	32	18.4	(9.94–34.1)
<20 cigarrettes/day	69	11	0.82	(0.43–1.59)	18	14.6	(7.26–29.5)
≥20 cigarrettes/day	32	12	1.76	(0.88–3.50)	14	26.4	(11.7–59.8)
Occupation							
White-collar workers	1062	198	1.00	–	48	1.00	–
Blue-collar workers	127	42	1.85	(1.26–2.72)	9	1.67	(0.79–3.52)
Prior lung diseases							
No	1154	223	1.00	–	50	1.00	–
Yes	35	17	2.45	(1.33–4.49)	7	4.61	(1.91–11.1)

[a]Adjusted for age (continuous), and year and season of questionnaire study.

(Table 2B). In contrast, an increased OR (2.83; 95% CI = 1.02–7.82) for squamous cell and small cell carcinoma was found in females who consumed dried/salted fish frequently ($P = 0.056$ for trend). Frequent consumption of soybean curds lowered the ORs for adenocarcinomas ($P = 0.021$ for trend), but not for squamous cell and small cell carcinomas ($P = 0.519$ for trend). Decreased ORs with vegetable and fruit consumption were not apparent for either histological type, except for decrease in ORs for adenocarcinomas with carrot consumption. Frequent consumption of pickled Chinese cabbage revealed an increasing trend of the ORs for squamous cell and small cell carcinomas ($P = 0.033$).

DISCUSSION

The present study revealed decreased ORs for adenocarcinoma of the lung with frequent consumption of cooked/raw fish in both male and female Japanese.

Table 2A Estimated odds ratios (ORs) and 95% confidence intervals (CIs) for patients with lung cancer according to food consumption by hitopathological type in males

	Adenocarcinomas (*n* = 367)					Squamous cell and small cell carcinomas (*n* = 381)				
	Consumption quartile					Consumption quartile				
	1 (lowest)	2	3	4 (highest)	*P* for trend	1 (lowest)	2	3	4 (highest)	*P* for trend
	OR[a]	OR[a] (95% CI)	OR[a] (95% CI)	OR[a] (95% CI)		OR[a]	OR[a] (95% CI)	OR[a] (95% CI)	OR[a] (95% CI)	
Vegetables and fruit										
Raw vegetables[b]	1.00	1.13 (0.69–1.85)	1.13 (0.69–1.86)	1.01 (0.62–1.65)	0.662	1.00	1.31 (0.84–2.03)	0.70 (0.44–1.12)	0.80 (0.51–1.25)	0.004
Fruit[b]	1.00	1.17 (0.75–1.85)	1.02 (0.63–1.65)	0.98 (0.61–1.58)	0.383	1.00	0.88 (0.58–1.34)	0.81 (0.52–1.26)	0.61 (0.40–0.95)	0.007
Green vegetables[c]	1.00	1.21 (0.88–1.67)	0.90 (0.63–1.28)	0.77 (0.51–1.15)	0.041	1.00	0.95 (0.69–1.30)	0.90 (0.64–1.27)	0.49 (0.32–0.74)	0.002
Carrot[c]	1.00	1.27 (0.97–1.65)	1.04 (0.71–1.51)	1.08 (0.67–1.76)	0.636	1.00	1.00 (0.76–1.31)	1.61 (1.12–2.31)	1.49 (0.94–2.36)	0.020
Pumpkin[c]	1.00	1.23 (0.96–1.59)	0.87 (0.49–1.53)	0.84 (0.32–2.16)	0.681	1.00	1.20 (0.93–1.57)	1.67 (1.06–2.62)	1.23 (0.55–2.77)	0.036
Pickles of Chinese cabbages[d]	1.00	0.90 (0.67–1.22)	0.91 (0.68–1.23)	0.82 (0.58–1.17)	0.297	1.00	1.18 (0.85–1.62)	1.22 (0.89–1.66)	1.39 (0.99–1.93)	0.056
Vegetable pickles lightly preserved[d]	1.00	0.79 (0.55–1.11)	0.91 (0.66–1.26)	0.71 (0.51–1.01)	0.125	1.00	0.54 (0.37–0.80)	0.70 (0.50–0.99)	0.93 (0.67–1.28)	0.865
Meat, milk and egg										
Beef[d]	1.00	1.23 (0.82–1.85)	1.36 (0.92–2.03)	1.07 (0.62–1.83)	0.426	1.00	1.10 (0.74–1.62)	1.15 (0.78–1.69)	1.08 (0.64–1.81)	0.625
Pork[d]	1.00	1.09 (0.77–1.53)	1.07 (0.75–1.53)	0.92 (0.54–1.56)	0.917	1.00	1.13 (0.80–1.59)	1.05 (0.73–1.50)	1.39 (0.85–2.27)	0.416
Chicken[d]	1.00	0.77 (0.53–1.13)	0.95 (0.66–1.36)	0.64 (0.41–1.02)	0.320	1.00	0.75 (0.51–1.10)	0.86 (0.60–1.24)	0.84 (0.55–1.28)	0.769
Milk[e]	1.00	0.96 (0.72–1.28)	0.92 (0.68–1.24)	0.82 (0.52–1.30)	0.390	1.00	0.87 (0.65–1.16)	0.76 (0.57–1.03)	0.66 (0.41–1.05)	0.030
Egg[c]	1.00	1.24 (0.83–1.86)	1.08 (0.71–1.64)	1.10 (0.73–1.64)	0.826	1.00	1.38 (0.87–2.18)	1.88 (1.19–2.95)	1.62 (1.04–2.54)	0.030
Fish										
Cocked/raw fish[c]	1.00	0.83 (0.61–1.13)	0.89 (0.63–1.25)	0.51 (0.31–0.84)	0.039	1.00	0.94 (0.68–1.29)	0.95 (0.66–1.36)	0.63 (0.40–1.01)	0.112
Dried/salted fish[d]	1.00	0.86 (0.60–1.22)	1.11 (0.79–1.57)	0.66 (0.41–1.07)	0.743	1.00	1.17 (0.81–1.71)	1.21 (0.84–1.76)	1.37 (0.89–2.12)	0.172
Soybean products										
Soybean curds (tofu)[c]	1.00	1.33 (0.95–1.87)	1.27 (0.88–1.84)	1.24 (0.83–1.85)	0.478	1.00	1.10 (0.78–1.55)	1.09 (0.76–1.57)	1.23 (0.84–1.81)	0.341
Miso soup[e]	1.00	1.93 (0.90–4.14)	1.65 (0.78–3.51)	1.40 (0.63–3.11)	0.346	1.00	2.24 (0.98–5.11)	2.40 (1.07–5.38)	2.50 (1.08–5.79)	0.112
Beverages										
Green tea[f]	1.00	1.06 (0.72–1.57)	1.11 (0.74–1.66)	1.33 (0.83–2.15)	0.250	1.00	0.99 (0.67–1.47)	1.17 (0.78–1.73)	1.08 (0.66–1.75)	0.443
Coffee[g]	1.00	0.85 (0.61–1.19)	0.87 (0.60–1.25)	1.18 (0.80–1.74)	0.654	1.00	0.98 (0.70–1.37)	1.15 (0.80–1.64)	1.61 (1.09–2.39)	0.027

[a]Adjusted for age (continuous), season and year of visit, occupation, prior lung diseases, smoking (never, former, current [<20 cigarettes/day] and current [≥20 cigarettes/day]), and consumption of green vegetables and meat. Quartiles are [b]almost never; occasionally, 3–4 times/week, and everyday; [c]<1 time/week, 1–2 time/week, 3–4 times/week, and ≥5 times/week; [d]almost never, 1–3 time/month, 1–2 times/week, and ≥3 times/week; [e]almost never, occasionally, 1 time/day, and ≥2 times/day; [f]<1 cup/day, 1 cup/day, 2 cups/day, and ≥7 cups/day; [g]<1 cup/day, 1–3 cups/day, 4–6 cups/day, and ≥3 cups/day.

Table 2B Estimated odds ratios (ORs) and 95% confidence intervals (CIs) for patients with lung cancer according to food consumption by hitopathological type in females

	Adenocarcinomas (n = 367)					Squamous cell and small cell carcinomas (n = 381)				
	Consumption quartile					Consumption quartile				
	1 (lowest)	2	3	4 (highest)	P for trend	1 (lowest)	2	3	4 (highest)	P for trend
	OR[a]	OR[a] (95% CI)	OR[a] (95% CI)	OR[a] (95% CI)		OR[a]	OR[a] (95% CI)	OR[a] (95% CI)	OR[a] (95% CI)	
Vegetables and fruit										
Raw vegetables[b]	1.00	0.74 (0.39–1.41)	0.85 (0.45–1.60)	0.84 (0.45–1.55)	0.904	1.00	0.97 (0.26–3.55)	2.11 (0.61–7.34)	1.01 (0.28–3.58)	0.896
Fruit[b]	1.00	0.71 (0.28–1.82)	0.78 (0.31–1.97)	0.68 (0.27–1.70)	0.536	1.00	0.50 (0.11–2.31)	0.34 (0.07–1.60)	0.49 (0.11–2.13)	0.668
Green vegetables[c]	1.00	0.83 (0.47–1.45)	1.09 (0.63–1.88)	0.64 (0.36–1.15)	0.230	1.00	0.83 (0.28–2.42)	1.00 (0.34–2.89)	1.37 (0.46–4.09)	0.310
Carrot[c]	1.00	0.76 (0.49–1.19)	0.70 (0.43–1.12)	0.50 (0.29–0.86)	0.014	1.00	1.05 (0.46–2.41)	0.51 (0.19–1.40)	0.47 (0.16–1.43)	0.080
Pumpkin[c]	1.00	0.93 (0.67–1.28)	1.02 (0.66–1.58)	0.64 (0.28–1.48)	0.555	1.00	0.81 (0.40–1.63)	0.78 (0.30–2.01)	1.18 (0.32–4.30)	0.816
Pickles of Chinese cabbages[d]	1.00	0.73 (0.50–1.08)	0.87 (0.59–1.30)	0.81 (0.54–1.23)	0.308	1.00	1.12 (0.48–2.62)	1.79 (0.79–4.08)	2.18 (0.99–4.82)	0.033
Vegetables pickles lightly preserved[d]	1.00	1.20 (0.77–1.88)	1.16 (0.75–1.80)	1.04 (0.68–1.58)	0.979	1.00	0.63 (0.20–2.01)	2.01 (0.80–5.02)	1.27 (0.50–3.20)	0.264
Meat, milk and egg										
Beef[d]	1.00	1.11 (0.71–1.73)	1.20 (0.78–1.85)	1.07 (0.59–1.94)	0.585	1.00	0.87 (0.38–1.99)	0.71 (0.30–1.64)	1.06 (0.35–3.22)	0.709
Pork[d]	1.00	1.07 (0.68–1.67)	1.13 (0.73–1.75)	0.80 (0.45–1.43)	0.710	1.00	0.78 (0.34–1.79)	0.85 (0.37–1.97)	0.48 (0.14–1.69)	0.370
Chicken[d]	1.00	1.18 (0.66–2.11)	1.06 (0.62–1.83)	0.94 (0.52–1.70)	0.536	1.00	0.66 (0.23–1.87)	0.99 (0.40–2.44)	0.75 (0.26–2.16)	0.900
Milk[e]	1.00	0.81 (0.53–1.25)	0.96 (0.64–1.43)	0.67 (0.40–1.11)	0.314	1.00	1.34 (0.59–3.05)	1.12 (0.49–2.60)	0.87 (0.31–2.46)	0.789
Egg[e]	1.00	1.40 (0.83–2.37)	1.15 (0.68–1.95)	1.05 (0.62–1.78)	0.463	1.00	1.21 (0.46–3.19)	1.16 (0.43–3.12)	1.06 (0.40–2.76)	0.965
Fish										
Cooked/raw fish[c]	1.00	0.97 (0.66–1.43)	0.80 (0.51–1.24)	0.48 (0.24–0.94)	0.028	1.00	0.93 (0.44–1.99)	0.56 (0.22–1.42)	0.97 (0.28–3.30)	0.404
Dried/salted fish[d]	1.00	0.67 (0.44–1.01)	0.66 (0.44–0.99)	0.79 (0.47–1.34)	0.274	1.00	0.99 (0.38–2.55)	1.15 (0.47–2.84)	2.83 (1.02–7.82)	0.056
Soybean products										
Soybean curds (tofu)[c]	1.00	0.89 (0.55–1.43)	0.93 (0.56–1.52)	0.52 (0.30–0.91)	0.021	1.00	3.68 (0.99–13.6)	2.86 (0.73–11.2)	3.00 (0.72–12.6)	0.519
Miso soup[e]	1.00	0.79 (0.36–1.72)	0.90 (0.42–1.93)	0.69 (0.30–1.59)	0.690	1.00	0.51 (0.12–2.07)	0.45 (0.11–1.77)	0.51 (0.11–2.42)	0.556
Beverages										
Green tea[f]	1.00	0.98 (0.58–1.66)	1.14 (0.68–1.93)	1.14 (0.61–2.12)	0.464	1.00	0.36 (0.14–0.93)	0.41 (0.16–1.04)	0.49 (0.17–1.46)	0.282
Coffee[g]	1.00	0.76 (0.51–1.13)	0.82 (0.49–1.35)	1.28 (0.65–2.54)	0.823	1.00	0.96 (0.43–2.18)	0.61 (0.21–1.78)	0.28 (0.05–1.58)	0.142

aAdjusted for age (continuous), season and year of visit, occupation, prior lung diseases, smoking (never, former, current [<20 cigarettes/day] and current [≥20 cigarettes/day]), passive smoking from husband (never, former and current), and consumption of green vegetables and meat. Quartiles are balmost never; occasionally, 3–4 times/week, and everyday; c<1 time/week, 1–2 time/week, 3–4 times/week, and ≥5 times/week; dalmost never, 1–3 time/month, 1–2 times/week, and ≥3 times/week; ealmost never, occasionally, 1 time/day, and ≥2 times/day; f<1 cup/day, 1–3 cups/day, 4–6 cups/day, and ≥7 cups/day; g<1 cup/day, 1 cup/day, 2 cups/day, and ≥3 cups/day.

Previous epidemiological studies showed inconsistent results for the association between fish consumption and risk of lung cancer. A study in Norway found a negative association between cod liver oil supplement and lung cancer risk, due to high intake of vitamin A and n-3 PUFA (Veierod et al, 1997). A decreased OR was observed in female nonsmokers of Hong Kong (Koo, 1988) and in males of Australia (Pierce et al, 1989), although the numbers of cases were small. On the other hand, fish consumption was associated with increased OR for lung cancer in males of Yunnan, China, where average consumption of fish in controls was very low (Swanson et al, 1992). Moreover, 2 cohort and 2 case-control studies found no association (Kvale et al, 1983; Knekt et al, 1991; Goodman et al, 1992; Sankaranarayanan et al, 1994). Fish consumption was, however, inversely associated with male lung cancer mortality in countries with high levels of cigarette smoking or animal fat consumption in a recent ecological study (Zhang et al, 2000). Of 36 countries, Japan with lower mortality rate of lung cancer showed higher consumption of cigarette smoking and fish, but lower animal fat intake.

Cyclo oxygenase-2 (COX-2) is a key inducible enzyme in arachidonic acid metabolism, and experimental and pathological studies have provided evidence of an involvement of COX-2 in carcinogenesis, in addition to inflammatory reactions (Vane, 1994; Oshima et al, 1996). N-3 PUFA inhibits arachidonic acid metabolism through a mechanism different from that with COX-2 inhibitors, but also modulates tmorigenesis (Karmali, 1987; Vane, 1994). Recent studies found an increase in COX-2 expression in human lung cancer, specifically in adenocarcinomas (Hida et al, 1998; Wolff et al, 1998). The results of our study and previous investigators suggest that effects of fish consumption and COX-2 inhibitors are more pronounced for adenocarcinomas than other histological types.

The fact that dried/salted fish consumption was not associated with any decrease in the OR for lung cancer requires explanation. Fish oil demonstrates rapid degradation due to oxidation and other chemical changes on exposure to air, light and heat (Frankel, 1980; Porter et al, 1995). Dried/salted fish is a preserved food, which is consumed several days at least after processing of raw fish. Decreased concentrations of n-3 PUFAs might therefore be expected. Furthermore, a positive association between preserved food consumption and lung cancer risk has been reported (Koo, 1988; Sankaranarayanan et al, 1994; Wakai et al, 1999a). Oxidized n3-PUFA and various contaminants in preserved dried/salted fish might have been linked to the increased OR observed for female cases with squamous cell and small cell carcinomas. An increased OR was also observed for those who consumed another preserved food, pickled Chinese cabbage. Smoking was not associated, because smoking habit was not related to food consumption in female controls and similar results were obtained with and without adjustment for smoking (data not shown).

Previous studies have demonstrated an inverse association between soybean consumption and lung cancer risk in non-smoking female cases with adenocarcinomas or large cell carcinomas in Hong Kong (Koo, 1988), in male cases of Yunnan (Swanson et al, 1992), in male and female cases of Shanghai (Ershow et al, 1990), and in male and female cases with squamous cell carcinoma in Japan (Wakai et al, 1999a). The present results were partially concordant with the first study. Isoflavones of soybean products have not only anti-oestrogenic and oestrogenic effects, but also non-oestrogenic inhibitory influence on tumour development (messina et al, 1994). Risk reduction for female adenocarcinomas seems to be related to hormone effects. However, the disconcordant results by gender and histological type between studies means that this issue is still controversial.

Miso soup consumption tended in the present study to be associated with an increased risk of squamous cell and small cell carcinomas in males. Miso is not only another source of isoflavones, but also a preserved food that contains nitrosamine precursors (Wakai et al, 1999b). The present result was partially in line with a previous study, showing risk elevation in males and females (Wakai et al, 1999a).

Protective effects of vegetables and fruit consumption have been addressed in numerous studies (World Cancer Research Fund, 1997). Some authors have found obvious risk reduction in smokers (Kvale et al, 1983; Voorrips et al, 2000), concordant with our results for male cases with squamous cell and small cell carcinomas. On the other hand, increased ORs for squamous cell and small cell carcinomas were observed in males who frequently consumed carrot and pumpkin rich in beta-carotene. Recent clinical trials of supplemental beta-carotene did not result risk reduction of lung cancer, but rather an elevation of risk (The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group, 1994; Hennekens et al, 1996; Omenn et al, 1996). Intake doses of beta-carotene in these studies were much higher than usual consumption from foods. It is possible that our results still included residual confounding by smoking after the adjustment, because consumption of carrot ($R^2 = 0.20$) and pumpkin ($R^2 = 0.20$) was more strongly correlated to the smoking habit than other vegetables and fruit in our controls. Such a correlation was also observed in coffee drinkers ($R^2 = 0.25$). Some studies have shown a positive association between coffee consumption and lung cancer risk, although the possibility of the residual confounding by smoking remains (World Cancer Research Fund, 1997).

A positive association between dietary fat and lung cancer risk has been reported for Western countries (World Cancer Research Fund, 1997), the association being more consistent for consumption of saturated/animal fat and cholesterol. The present study did not reveal a positive association between meat consumption and lung cancer risk, except for an increased OR for male squamous cell and small cell carcinomas with frequent consumption of eggs rich in cholesterol. To clarify this situation, further investigations of dietary fat by nutrient are required, with adjustment for energy intake.

The decreased OR for squamous cell carcinoma for milk consumption was consistent with previous findings (Kvale et al, 1983). A recent cohort study has also revealed risk reduction for lung cancer mortality with frequent dairy product consumption (Breslow et al, 2000), although other investigators have shown no association or increased risk (Koo, 1988; Goodman et al, 1992; Sankaranarayanan et al, 1994). Dairy products contain linoleic acid, sphingomyelins, butyric acid, retinal, calcium, and vitamin D, that have potential protective effects against tumorigenesis (Breslow et al, 2000).

A limitation of our present study was the lack of information on nutrient intake, especially for n-3 PUFA and n-6 PUFA. Whereas n-3 PUFA inhibits growth and promotion of tumours, n-6 PUFA could stimulate them (Karmali, 1987; DeVries and van Noorden, 1992; Vane, 1994). The n-6 PUFA/n-3 PUFA ratio is, therefore, an important additional factor for tumorigenesis (De Vries and van Noorden, 1992). However, an international ecological study revealed that Japanese consume much more n3-PUFA with a much lower ratio of n6 PUFA/n3 PUFA, compared with Western

countries (Hursting et al, 1990). Major contributors of n-3 PUFA intake are mixed salad oil, vegetable oil, mayonnaise, tofu (soybean curds), chicken eggs and fish among Japanese in the Tokai area (Tokudome et al, 1999), where we recruited our study subjects. These vegetable components and chicken eggs also contribute to n-6 PUFA intake, but this is less so for fish. Therefore, frequent consumption of fish can in this context be positively related not only to n-3 PUFA intake, but also a low ratio of n-6PUFA/n-3 PUFA.

Regarding methodological issues, selection bias needs consideration, since controls were recruited from non-cancer hospital outpatients. However, the distribution of diseases among randomly selected non-cancer controls of Aichi Cancer Center Hospital did not demonstrate any obvious feature in common, with reference to precancerous lesions or tobacco-related conditions (Inoue et al, 1995). Furthermore, to access the quality and validity of our questionnaire, we compared non-cancer ACCH outpatients with subjects randomly selected from the electoral roll (Inoue et al, 1997). We found that, with due consideration of age, sex, and season in the analysis, it is feasible to use non-cancer outpatients as controls.

In conclusion, our findings suggest the consumption of fish rich in n-3 PUFA modifies the risk of development of adenocarcinoma of the lung. This provides support for earlier epidemiological pointers to an involvement of n-3 PUFA in carcinogenesis. The relatively lower mortality rate of lung cancer in Japan might thus be at least partly attributable to higher consumption of fish.

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