

Dietary Habits and Risk of Lung Cancer Death in a Large-scale Cohort Study (JACC Study) in Japan by Sex and Smoking Habit

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Lung cancer has increased and is the leading cause of cancer death among Japanese males. The associations of dietary habits with the risk of lung cancer death were evaluated by sex and smoking habits in this study. In the Japan Collaborative Cohort (JACC) Study, a cohort established in 1988–90 and consisting of 42 940 males and 55 308 females was observed for lung cancer deaths up to the end of 1997. During the observation period, 446 males and 126 females died of lung cancer. A self-administered food frequency questionnaire was used as the baseline survey. Hazard ratios for dietary factors were calculated by Cox's proportional hazards model. Among males, a high intake of ham and sausages, cheese, green-leafy vegetables, oranges, and other fruits significantly and dose-dependently decreased the risk of lung cancer death. Among females, a high intake of miso-soup, ham and sausages, and liver significantly and almost dose-dependently increased the risk. Vegetables and fruits rich in antioxidative and carcinogenic agents reduced the risk of lung cancer deaths among male smokers more than among female nonsmokers. The results among female nonsmokers were partially consistent with the hypothesis that high fat consumption increases the risk of lung cancer, especially that of adenocarcinoma.

Key words: Diet — Lung cancer — Cohort study — Epidemiology

The associations between diet and lung cancer have been argued in numerous epidemiologic studies. A high consumption of green-yellow vegetables or fruits has been believed to reduce the risk of lung cancer although some β -carotene intervention studies resulted in failure.^{1–7)} It is considered that experimental mutagenesis and carcinogenesis in animals could be inhibited by a large number of compounds from edible plants, including carotenoids, polyphenols, thiols, trace metals, terpenes, tocopherols, and degradation products of glucosinolates.¹⁾ Recently, the protective activity of vegetables and fruits has been focused on antioxidative micronutrients such as carotenoids, vitamin C, folate and others, and recent studies have been focusing on the interactions among them.^{1–8)} Some studies reported that the protective effect of vegetables and fruits was stronger among current smokers than

among nonsmokers.^{9–11)} It is thought that antioxidants strongly reduce the oxidative stress due to smoking. However, among nonsmokers, the effect of antioxidants is relatively small because nonsmokers are under less oxidative stress, or their already low risk of lung cancer is not reduced further.^{9, 10)} It has been thought that high fat consumption increases the risk of lung cancer,^{1, 2)} but different effects of animal, plant and fish fats or oils remain to be argued.^{12, 13)}

In Japan, Hirayama's study has been the only large-scale cohort study for evaluating lifestyles and cancer risk; it started in 1965 and was completed around 20 years ago.¹⁴⁾ Diet was examined in that study, but the diet of Japanese people has rapidly changed since the Hirayama's study. Fat consumption increased from 46.5 g per capita in 1965 to 58.3 g in 1988 and consumption of green-yellow vegetables also increased from 49.0 g to 72.8 g per capita. In contrast, consumption of cereals decreased from 418.5 g to 289.2 g per capita during the same period.¹⁵⁾ Recent

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case-control studies in Japan showed that raw vegetables and fruits reduced the lung cancer risk among smokers and ex-smokers¹⁶⁾ and that preserved foods increased, while soyfoods decreased, the risk of lung cancer.¹⁷⁾ Thus, a new, and more comprehensive cohort study is necessary to evaluate the dietary risk of cancer. The Japan Collaborative Cohort Study for Evaluation of Cancer Risk sponsored by Monbusho (JACC Study) was planned in the late 1980's as a new large-scale cohort study surveying people more comprehensively and detailing their lifestyles, while preserving sera of the participants in the baseline survey.¹⁸⁾ The new cohort consisted of people in various areas in Japan and was checked for deaths up to the end of 1997. In the present study, we examined the association of lung cancer death with the diet as surveyed by the baseline questionnaire, with special reference to the association by sex and smoking habits.

SUBJECTS AND METHODS

In the JACC Study, a cohort of 46 465 males and 64 327 females aged 40 to 79 years in 45 areas in Japan completed the baseline survey during 1988–1990.¹⁸⁾ The areas were selected from 19 prefectures throughout Japan. The cohort consisted of the whole general population (39% of the subjects in this present study), participants in health checkups for a local community (52% of them) and others (voluntary groups, etc.). A self-administered questionnaire for the survey included past and family histories, health conditions and lifestyle habits such as smoking, drinking, diet, physical exercise, occupation, and others. The same questionnaire was used in every area in this study in principle, but some questions differed by area for regional reasons.

As for diet, the questionnaire elicited the intake frequency of 32 food items and the number of dishes of boiled rice and miso-soup eaten a day. The subjects were asked about their average diet at the time of the baseline survey. The 32 items were beef, pork, ham and sausages, chicken, liver, egg, milk, yogurt, cheese, butter, margarine, fried foods, fried vegetables, fish (raw, grilled or boiled fish, excluding processed and preserved fish), boiled fish paste ('*kamaboko*' in Japanese), dried or salted fish, green-leafy vegetables, carrots and squash, tomatoes, cabbage and lettuce, Chinese cabbage, edible wild plants ('*sansai*' in Japanese), mushroom, potatoes, seaweed, pickles, foods boiled down in soy sauce ('*tsukudani*' in Japanese), boiled beans, tofu (soybean curd), oranges, fruits other than oranges, and fruit juice. There were five categories of frequency (scarcely any, 1–2 times a month, 1–2 times a week, 3–4 times a week, and almost every day).

Some questions about diet were not asked in some areas for regional reasons. The questions about 16 items (liver, cheese to fried vegetables, boiled fish paste, green-leafy

vegetables, Chinese cabbage, mushroom, foods boiled down in soy sauce to fruit juice, in the above list) were put to 83–88% of the subjects and the questions about other items were put to more than 90% of them.

The validity of this food frequency questionnaire was evaluated by comparing it with four 3-day dietary records for 8 males and 77 females selected from the study areas. Spearman's correlation coefficients for the frequencies were more than 0.6 for ham and sausages, milk and margarine, and less than 0.2 for liver, fried foods, fried vegetables, boiled fish paste, dried or salted fish, Chinese cabbage, wild edible plants, foods boiled down in soy sauce, and the other foods ranged between them (Date C. *et al.*, unpublished data).

For the present study, the subjects were limited to 42 940 males and 55 308 females who had no history of lung cancer and answered the question about their smoking status. Non-responders to the question about smoking status were 3.2% of the male subjects and 13.4% of the female subjects, probably because nonsmoking women seem to have less concern about the question on smoking. The subjects were checked for death using death certificates by permission of the Management and Coordination Agency of the Japanese Government from their entry into this study up to the end of 1997. All deceased people in the study areas and people who moved out of the study areas were identified using the population registry by permission of each municipality office. During the observation period, 1167 males (2.7%) and 1718 females (3.1%) were censored because they moved out of the study areas. A total 4864 males and 2953 females died, including those who died of lung cancer, during the period. The mean observation period was 92 months (SD; 21 months). Death from lung cancer was defined by the code 'C34' in the ICD-10 (International Statistical Classification of Diseases and Related Health Problems, Tenth Revision). The histologic type of lung cancer was rarely given on death certificates, so we analyzed lung cancer as a whole.

The subjects who died of lung cancer during the observation period were 446 males and 126 females. Table I shows the number of subjects and lung cancer cases by smoking status. The hazard ratios (HRs) for dietary risk factors were separately estimated among males and females, and then among smoking-status groups by sex (male current smokers, male ex-smokers and female non-smokers). The other smoking-status groups were not analyzed because of insufficient numbers of lung cancer cases. The ratios were adjusted for age (numeric), father's or mother's history of lung cancer (dichotomous), and in addition, smoking index (levels of <20, 20–39, 40–59, 60–79, 80–99 and 100+ pack-years) among current smokers, and the period after quitting smoking (levels of <5, 5–9, 10–14, 15–19 and 20+ years) among ex-smokers. All these factors were considered in calculating HRs

among males and females, respectively. Passive smoking at home was evaluated dichotomously in the questionnaire. The effect was not significant among female nonsmokers (HR=0.80, 95%CI; 0.49, 1.28). Consequently, it was not used in computing the adjusted HRs among them. The ratios were not adjusted for total energy or its surrogates because the subjects' diet was measured by a simple food frequency method for limited food items.

The five categories of food frequency, and quantity of boiled rice and miso-soup were integrated into three groups by considering the number of subjects in each group and a meaningful cut-off frequency. HRs of the highest and intermediate intake compared with the lowest were calculated with Cox's proportional hazards model using the PHREG procedure in the SAS package.¹⁹⁾ The HRs were obtained by stratification of 19 prefectures using the 'strata' statement of the procedure, because diet may differ by area. The dose-response trend was tested by evaluating the regression coefficient when the three intake categories were treated as equally-spaced numeric variables in the Cox model. *P* values less than 0.05 were considered significant. This investigation was approved by the Ethical Board of Nagoya University School of Medicine.

RESULTS

HRs of lung cancer deaths associated with diet are presented in Tables II to V, which show the items significant at the level of *P*<0.1 for at least one category (fish for males and females, oranges for male ex-smokers, and green-leafy vegetables and oranges for female nonsmokers are exceptions because the items are noteworthy). Among all males (Table II), a high intake of ham and sausages, cheese, green-leafy vegetables, oranges, and other fruits significantly and dose-dependently decreased the risk of lung cancer death. The HRs of the highest intakes compared with the lowest were 0.72 (95% CI; 0.52, 0.99) for ham and sausages, 0.59 (0.38, 0.91) for cheese, 0.76 (0.59, 0.98) for green-leafy vegetables, 0.75 (0.57, 0.99) for oranges, and 0.73 (0.55, 0.97) for other fruits. In addition, yogurt, butter, carrots and squash, tomatoes, boiled beans, and fruit juice, had significantly low HRs (range 0.70–0.74) for intermediate intake compared with the lowest. Among all females, a high intake of miso-soup, ham and sausages, and liver significantly and almost dose-dependently increased the risk (HR=1.92 (95%CI; 1.00, 3.67), 1.79 (1.07, 3.01), and 2.25 (1.02, 4.94) for the highest intake, respectively). Tofu had a significantly low HR (0.50) for the intermediate intake without dose-dependency.

Among male current smokers (Table III), a high intake of boiled rice in their 30s significantly and dose-dependently increased the risk of lung cancer death (HR=1.93, 95% CI; 1.11, 3.36, for the highest intake). A high intake

Table I. Number of Subjects, Observed Person-years and Cases Who Died of Lung Cancer in the Cohort Classified by Sex and Smoking Status

	Subjects	Person-years	Cases
Males			
Current smokers	22 465	180 309	303
Ex-smokers	11 308	89 864	111
Nonsmokers	9 167	74 566	32
Females			
Current smokers	2 868	23 123	19
Ex-smokers	852	6 683	6
Nonsmokers	51 588	421 547	101

of oranges and other fruits significantly and almost dose-dependently decreased the risk (HR=0.66 (95% CI; 0.47, 0.91), and 0.71 (0.50, 0.99) for the highest intake, respectively). Milk, yogurt, cheese, butter, carrots and squash, tomatoes, and fruit juice had significantly low HRs (range 0.64–0.70) for intermediate intake compared with the lowest.

Among male ex-smokers (Table IV), cheese consumption had an inverse association with lung cancer death (HR=0.24, 95% CI; 0.07, 0.81) for the highest intake vs. the lowest. Foods boiled down with soy sauce had a significantly high HR (1.76) for intermediate intake.

Among female nonsmokers (Table V), a high intake of ham and sausages significantly and dose-dependently increased the risk (HR=2.02 (95%CI; 1.15, 3.53) for the highest intake). Tofu had a significantly low HR (0.45) for the intermediate intake without dose-dependency.

Intake of other foods, not shown in Tables II to V, was not associated with lung cancer death among each group. In addition, excluding lung cancer deaths within two years after the baseline survey did not substantially alter the results.

DISCUSSION

The risk of lung cancer was evaluated for each sex and separately for groups classified by sex and smoking status in our study. The reason was, first, that the characteristics of lung cancer were associated with smoking status of the subjects. The proportions of squamous cell carcinoma, small cell carcinoma and adenocarcinoma cases ranged from 34.3 to 38.5%, from 12.6 to 15.5%, and from 29.2 to 41.4%, respectively, among males in the four cancer registries of Japan in 1987–1992.²⁰⁾ Among females, the corresponding proportions ranged from 8.5 to 13.8%, from 6.4 to 11.7%, and from 55.4 to 69.5%. This sex difference in distribution of histologic type is thought to reflect the difference in smoking rates by sex in Japan (60.5% for males

Table II. Hazard Ratios (HRs) of Lung Cancer Death for Diet and 95% Confidence Intervals (CIs) Adjusted by Age, Parents' History of Lung Cancer, Smoking Status, Smoking Index⁴⁾ and Time since Quitting Smoking

Item	Category	Males					Females				
		Person-years	Deaths	HR	95%CI	P	Person-years	Deaths	HR	95%CI	P
Boiled rice in the 30s	0-2 dishes/day	90 085	101	1.00			129 376	38	1.00		
	3-5 dishes/day	108 679	120	1.48	0.96-2.29	0.072	187 538	36	0.89	0.47-1.69	0.73
	6+ dishes/day	136 273	214	1.43	0.94-2.18	0.092	119 733	47	1.41	0.74-2.66	0.28
					trend P=0.54					trend P=0.20	
Miso-soup	<1 dish/day	113 683	146	1.00			163 159	40	1.00		
	1-2 dishes/day	134 802	173	1.06	0.82-1.36	0.63	196 119	24	1.47	0.92-2.33	0.10
	3+ dishes/day	73 032	102	1.14	0.83-1.57	0.38	57 712	20	1.92	1.00-3.67	0.047
					trend P=0.69					trend P=0.017	
Ham & sausages	≤1-2/m	137 613	192	1.00			184 513	45	1.00		
	1-2/w	108 510	116	0.90	0.71-1.52	0.42	141 279	33	1.19	0.74-1.90	0.45
	3-4/w+	56 234	54	0.72	0.52-0.99	0.044	70 457	26	1.79	1.07-3.01	0.026
					trend P=0.049					trend P=0.033	
Liver	≤1-2/m	187 313	212	1.00			259 337	55	1.00		
	1-2/w	32 033	35	0.82	0.55-1.22	0.33	36 445	10	1.26	0.62-2.56	0.50
	3-4/w+	33 901	40	0.78	0.47-1.29	0.34	40 261	18	2.25	1.02-4.94	0.043
					trend P=0.28					trend P=0.051	
Milk	Scarcely any	57 481	91	1.00			67 704	17	1.00		
	1-2/m to 3-4/w	141 154	146	0.76	0.58-1.01	0.066	172 431	53	1.35	0.76-2.41	0.30
	Almost every day	119 489	150	0.87	0.67-1.14	0.33	179 542	39	0.89	0.50-1.59	0.70
					trend P=0.48					trend P=0.39	
Yogurt	Scarcely any	164 351	203	1.00			170 855	50	1.00		
	1-2/m to 1-2/w	68 002	56	0.71	0.52-0.98	0.039	124 285	29	0.81	0.50-1.31	0.39
	3-4/w+	43 607	49	0.81	0.54-1.22	0.32	67 663	21	0.82	0.45-1.52	0.54
					trend P=0.14					trend P=0.45	
Cheese	Scarcely any	128 092	180	1.00			181 137	54	1.00		
	1-2/m to 1-2/w	124 424	112	0.71	0.55-0.92	0.0092	153 684	30	0.72	0.44-1.18	0.20
	3-4/w+	30 246	28	0.59	0.38-0.91	0.017	37 039	11	0.81	0.39-1.66	0.57
					trend P=0.0029					trend P=0.33	
Butter	Scarcely any	126 736	165	1.00			170 541	42	1.00		
	1-2/m to 1-2/w	111 309	95	0.71	0.54-0.92	0.011	142 007	37	1.24	0.78-1.98	0.35
	3-4/w+	42 272	57	0.92	0.65-1.30	0.66	55 622	14	0.90	0.46-1.77	0.77
					trend P=0.23					trend P=0.95	
Margarine	Scarcely any	101 451	135	1.00			111 237	30	1.00		
	1-2/m to 1-2/w	111 543	103	0.77	0.57-1.02	0.073	156 520	42	1.07	0.64-1.80	0.78
	3-4/w+	41 909	53	0.92	0.65-1.28	0.63	73 590	13	0.61	0.30-1.20	0.15
					trend P=0.41					trend P=0.19	
Fried foods	≤1-2/m	73 052	86	1.00			105 029	21	1.00		
	1-2/w	129 688	150	0.99	0.76-1.29	0.95	175 753	46	1.48	0.88-2.49	0.13
	3-4/w+	74 575	97	1.12	0.82-1.51	0.45	88 868	28	1.77	0.98-3.18	0.056
					trend P=0.45					trend P=0.055	
Fried vegetables	≤1-2/m	62 731	80	1.00			77 268	20	1.00		
	1-2/w	126 008	126	0.78	0.59-1.04	0.095	163 014	51	1.36	0.81-2.30	0.24
	3-4/w+	93 108	136	1.02	0.77-1.36	0.84	134 695	27	0.88	0.48-1.61	0.69
					trend P=0.57					trend P=0.56	
Fish	≤1-2/w	150 457	184	1.00			187 845	59	1.00		
	3-4/w	85 300	112	1.12	0.87-1.43	0.36	119 381	24	0.73	0.45-1.21	0.23
	Almost every day	69 552	91	1.03	0.79-1.34	0.81	95 004	22	0.88	0.52-1.49	0.64
					trend P=0.72					trend P=0.50	

Table II. (Continued)

Item	Category	Males					Females				
		Person-years	Deaths	HR	95%CI	P	Person-years	Deaths	HR	95%CI	P
Fish paste (<i>Kamaboko</i>)	≤1-2/m	161 534	201	1.00			200 482	52	1.00		
	1-2/w	78 613	83	0.84	0.64-1.09	0.19	108 330	30	1.12	0.71-1.78	0.60
	3-4/w+	36 766	38	0.73	0.51-1.05	0.093	49 121	19	1.58	0.91-2.73	0.099
					trend P=0.056					trend P=0.12	
Green-leafy vegetables	≤1-2/w	124 585	164	1.00			141 206	32	1.00		
	3-4/w	93 429	118	0.90	0.71-1.14	0.40	126 177	35	1.18	0.73-1.91	0.48
	Almost every day	91 722	106	0.76	0.59-0.98	0.034	133 889	41	1.19	0.75-1.90	0.44
					trend P=0.035					trend P=0.45	
Carrots & squash	≤1-2/m	66 639	96	1.00			47 760	11	1.00		
	1-2/w	106 671	114	0.71	0.54-0.94	0.017	131 903	36	1.33	0.67-2.62	0.41
	3-4/w+	104 878	137	0.84	0.64-1.10	0.22	198 034	52	1.24	0.64-2.41	0.51
					trend P=0.35					trend P=0.69	
Tomatoes	≤1-2/m	124 840	163	1.00			131 978	36	1.00		
	1-2/w	90 808	85	0.70	0.54-0.92	0.010	117 262	22	0.75	0.44-1.28	0.30
	3-4/w+	81 190	114	0.90	0.70-1.16	0.43	142 617	47	1.21	0.76-1.94	0.40
					trend P=0.32					trend P=0.37	
Seaweed	≤1-2/w	140 174	188	1.00			143 102	43	1.00		
	3-4/w	89 630	105	0.86	0.68-1.10	0.24	123 558	31	0.88	0.55-1.41	0.62
	Almost every day	79 760	93	0.78	0.60-1.00	0.057	141 291	34	0.77	0.49-1.23	0.28
					trend P=0.049					trend P=0.28	
Boiled beans	≤1-2/m	153 868	187	1.00			191 543	47	1.00		
	1-2/w	64 811	66	0.74	0.56-0.99	0.043	89 205	23	0.96	0.58-1.60	0.89
	3-4/w+	44 528	62	0.90	0.67-1.21	0.51	73 650	17	0.81	0.46-1.44	0.47
					trend P=0.26					trend P=0.50	
Tofu (soybean curd)	≤1-2/w	108 467	149	1.00			121 809	41	1.00		
	3-4/w	84 667	94	0.80	0.62-1.04	0.10	115 861	18	0.50	0.28-0.88	0.016
	Almost every day	72 837	93	0.83	0.63-1.08	0.17	120 920	32	0.85	0.52-1.37	0.51
					trend P=0.14					trend P=0.43	
Oranges	≤1-2/m	59 999	87	1.00			46 440	12	1.00		
	1-2/w	68 496	86	0.88	0.65-1.19	0.41	73 087	16	0.92	0.43-1.97	0.84
	3-4/w+	131 490	148	0.75	0.57-0.99	0.045	236 107	64	1.10	0.58-2.09	0.76
					trend P=0.041					trend P=0.63	
Fruits other than oranges	≤1-2/m	47 428	81	1.00			36 480	13	1.00		
	1-2/w	70 508	78	0.71	0.52-0.98	0.038	67 655	15	0.71	0.33-1.51	0.38
	3-4/w+	130 690	141	0.73	0.55-0.97	0.029	234 644	56	0.80	0.42-1.50	0.49
					trend P=0.049					trend P=0.66	
Fruit juice	≤1-2/m	97 243	139	1.00			133 242	33	1.00		
	1-2/w	61 087	53	0.70	0.51-0.96	0.030	72 692	18	1.16	0.65-2.07	0.60
	3-4/w+	77 128	91	0.90	0.69-1.18	0.45	112 644	24	0.95	0.56-1.63	0.87
					trend P=0.35					trend P=0.90	

Abbreviations: 1-2/m=once or twice a month, 1-2/w=once or twice a week, 3-4/w=3-4 times a week.

a) Smoking index=quantity of cigarettes smoked per day × duration of smoking (year), for current smokers.

and 14.3% for females in 1990)²¹) and that in association of smoking and lung cancer by histologic type.²²) Squamous cell carcinoma, small cell carcinoma and adenocarcinoma accounted for 42.6%, 15.9% and 34.4% of lung cancer in male current smokers, respectively. The corresponding proportions were 51.8%, 14.6% and 30.7% for

male ex-smokers and 10.3%, 6.3% and 78.9% for female nonsmokers (recalculated from Sobue's data²²). Therefore, a high proportion of squamous cell and small cell carcinoma compared with adenocarcinoma for male current and ex-smokers could be assumed in our cohort, with the opposite distribution for female nonsmokers.

Table III. Hazard Ratios (HRs) of Lung Cancer Death for Diet and 95% among Male Current Smokers

Item	Category	Person-years	Deaths	HR	95%CI	P
Boiled rice in the 30s	0-2 dishes/day	47 402	56	1.00		
	3-5 dishes/day	59 232	81	1.82	1.03-3.21	0.038
	6+ dishes/day	69 762	159	1.93	1.11-3.36	0.018
					trend P=0.043	
Ham & sausages	≤1-2/m	73 539	143	1.00		
	1-2/w	56 590	71	0.77	0.58-1.04	0.090
	3-4/w+	29 309	36	0.68	0.46-1.00	0.050
					trend P=0.026	
Milk	Scarcely any	34 247	72	1.00		
	1-2/m to 3-4/w	77 419	95	0.70	0.50-0.97	0.036
	Almost every day	55 272	96	0.86	0.63-1.18	0.36
					trend P=0.48	
Yogurt	Scarcely any	90 449	145	1.00		
	1-2/m to 1-2/w	32 869	33	0.64	0.42-0.97	0.035
	3-4/w+	21 494	28	0.69	0.41-1.18	0.18
					trend P=0.069	
Cheese	Scarcely any	68 627	124	1.00		
	1-2/m to 1-2/w	63 815	68	0.67	0.49-0.92	0.015
	3-4/w+	16 203	23	0.76	0.46-1.25	0.28
					trend P=0.057	
Butter	Scarcely any	65 680	113	1.00		
	1-2/m to 1-2/w	58 811	61	0.65	0.47-0.90	0.011
	3-4/w+	23 006	40	0.94	0.62-1.42	0.77
					trend P=0.29	
Green-leafy vegetables	≤1-2/w	69 399	111	1.00		
	3-4/w	48 247	82	0.98	0.73-1.30	0.91
	Almost every day	44 960	70	0.80	0.59-1.09	0.17
					trend P=0.18	
Carrots & squash	≤1-2/m	69 192	69	1.00		
	1-2/w	47 099	76	0.69	0.49-0.96	0.030
	3-4/w+	39 849	92	0.86	0.62-1.19	0.38
					trend P=0.51	
Tomatoes	≤1-2/m	36 038	116	1.00		
	1-2/w	36 463	57	0.68	0.49-0.94	0.019
	3-4/w+	64 203	78	0.91	0.67-1.23	0.54
					trend P=0.42	
Oranges	≤1-2/m	28 707	69	1.00		
	1-2/w	38 929	58	0.78	0.55-1.11	0.17
	3-4/w+	63 294	94	0.66	0.47-0.91	0.012
					trend P=0.013	
Fruits other than oranges	≤1-2/m	52 021	61	1.00		
	1-2/w	31 869	56	0.70	0.49-1.02	0.065
	3-4/w+	40 105	90	0.71	0.50-0.99	0.044
					trend P=0.062	
Fruit juice	≤1-2/m	51 846	96	1.00		
	1-2/w	31 773	34	0.66	0.44-0.98	0.040
	3-4/w+	40 003	62	0.91	0.66-1.26	0.58
					trend P=0.46	

Abbreviations: 1-2/m=once or twice a month, 1-2/w=once or twice a week, 3-4/w=3-4 times a week. HRs were adjusted by age, parents' history of lung cancer and smoking index.

Second, diet is thought to interact with smoking. Smoking is the strongest lifestyle risk factor for lung cancer. Tobacco and tobacco smoke contain many tumorigenic agents such as polynuclear aromatic hydrocarbons, N-

nitrosamines, aromatic amines, and other organic and inorganic compounds.²³⁾ In addition, free radicals and single oxygen derived from cigarette smoke produce carcinogenic oxidative stress.^{7,8)} Fruits and vegetables are

Table IV. Hazard Ratios (HRs) of Lung Cancer Death for Diet and 95% Confidence Intervals (CIs) among Male Ex-smokers

Item	Category	Person-years	Deaths	HR	95%CI	P
Boiled rice at present	0–2 dishes/day	21 867	36	1.00		
	3–5 dishes/day	53 522	65	0.80	0.52–1.22	0.30
	6+ dishes/day	11 544	7	0.45	0.19–1.06	0.069
					trend $P=0.068$	
Cheese	Scarcely any	32 069	45	1.00		
	1–2/m to 1–2/w	33 859	31	0.69	0.42–1.15	0.16
	3–4/w+	7 392	3	0.24	0.07–0.81	0.022
					trend $P=0.013$	
Dried or salted fish	≤1–2/m	24 291	21	1.00		
	1–2/w	29 537	42	1.64	0.96–2.82	0.069
	3–4/w+	22 111	25	1.24	0.68–2.27	0.46
					trend $P=0.52$	
Green-leafy vegetables	≤1–2/w	30 394	40	1.00		
	3–4/w	25 199	30	0.82	0.51–1.33	0.43
	Almost every day	25 549	26	0.65	0.39–1.07	0.091
					trend $P=0.096$	
Foods boiled down with soy sauce (<i>tsukudani</i>)	≤1–2/m	36 084	31	1.00		
	1–2/w	19 372	29	1.76	1.05–2.93	0.030
	3–4/w+	14 121	14	1.07	0.56–2.04	0.81
					trend $P=0.47$	
Oranges	≤1–2/m	12 916	13	1.00		
	1–2/w	17 136	22	1.39	0.70–2.79	0.34
	3–4/w+	36 998	42	1.22	0.64–2.33	0.53
					trend $P=0.67$	

Abbreviations: 1–2/m=once or twice a month, 1–2/w=once or twice a week, 3–4/w=3–4 times a week. HRs were adjusted by age, parents' history of lung cancer and time since quitting smoking.

rich in antioxidant micronutrients such as carotenoids as well as other anti-carcinogenic agents.¹⁾ Therefore, protection is thought to work more effectively among smokers than among nonsmokers.^{9,10)}

Diet is confounded with smoking. Foods that were regarded as good for health were more frequently eaten by nonsmokers than smokers. For example, the subjects who drank milk almost every day were 34% of current smokers, 43% of ex-smokers, and 44% of nonsmokers among male subjects in this study, and they were 31%, 42%, and 44%, respectively, among females. The subjects eating oranges 3–4 times a week or more frequently were 47% of current smokers, 55% of ex-smokers, and 52% of nonsmokers among males, and they were 56%, 62%, and 67% among females. Other dairy foods, fruits, and green-yellow vegetables showed similar findings. The difference in intake of those foods within each smoking status was smaller than the difference by smoking status (see above). The subjects who drank milk almost every day were from 33% to 37% at various smoking index levels among male current smokers. Those eating oranges 3–4 times a week or more frequently were from 45% to 50%. Other dairy foods, fruits, and green-yellow vegetables also showed similar findings, and those proportions were less dose-

dependent on smoking index. Therefore, residual confounding by smoking on these foods was thought to be small.

This cohort consisted of the respondents to the questionnaire survey from the whole general population and participants in health checkups. This means that this cohort may be more health-conscious and have better lifestyles than the general population itself. This bias could make it difficult to detect the protective effect of good lifestyles. In this cohort, health-conscious people tended to eat more dairy products and green-yellow vegetables. For example, the subjects who drank milk almost every day were 46% of those taking a great interest in health checkup (answer to another question in this cohort questionnaire) among the male subjects in this current study, compared with 36% of those taking no interest. Among the female subjects, the corresponding values were 53% and 36%. Those eating green-leafy vegetables almost every day were 33% and 27%, among males, and 40% and 33% among females, respectively. Other dairy foods and green-yellow vegetables showed similar findings.

The protective effect of higher intake of fruits and vegetables for lung cancer is widely accepted, despite the negative results in β -carotene intervention studies.^{1,3–7)} The

Table V. Hazard Ratios (HRs) of Lung Cancer Death for Diet and 95% Confidence Intervals (CIs) among Female Nonsmokers

Item	Category	Person-years	Deaths	HR	95%CI	P
Miso-soup	<1 dish/day	147 825	30	1.00		
	1-2 dishes/day	186 192	48	1.51	0.89-2.56	0.12
	3+ dishes/day	55 440	16	1.77	0.85-3.71	0.12
trend P=0.059						
Ham & sausages	≤1-2/m	171 838	34	1.00		
	1-2/w	132 680	28	1.23	0.73-2.06	0.42
	3-4/w+	65 768	24	2.02	1.15-3.53	0.013
trend P=0.017						
Liver	≤1-2/m	243 103	43	1.00		
	1-2/w	33 626	9	1.43	0.66-3.02	0.42
	3-4/w+	36 529	15	2.29	0.95-5.47	0.062
trend P=0.061						
Fried foods	≤1-2/m	96 003	15	1.00		
	1-2/w	165 130	35	1.47	0.79-2.70	0.21
	3-4/w+	83 589	24	1.91	0.98-3.72	0.057
trend P=0.056						
Green-leafy vegetables	≤1-2/w	130 087	23	1.00		
	3-4/w	118 378	27	1.19	0.68-2.09	0.52
	Almost every day	126 081	35	1.35	0.79-2.30	0.26
trend P=0.26						
Tofu (soybean curd)	≤1-2/w	112 025	30	1.00		
	3-4/w	109 028	13	0.45	0.23-0.86	0.016
	Almost every day	115 137	29	0.90	0.53-1.53	0.71
trend P=0.70						
Oranges	≤1-2/m	42 090	8	1.00		
	1-2/w	68 271	12	0.95	0.38-2.34	0.91
	3-4/w+	223 275	53	1.18	0.54-2.57	0.66
trend P=0.053						

Abbreviations: 1-2/m=once or twice a month, 1-2/w=once or twice a week, 3-4/w=3-4 times a week. HRs were adjusted by age and parents' history of lung cancer.

discrepancy between the observation studies and intervention could be explained by the possibility that the excessive doses of β-carotene given in those intervention studies may be carcinogenic *in vivo*, and that the cooperative action of carotenoids and other compounds in fruits and vegetables is necessary to inhibit carcinogenesis.^{1,3-7)} Recently, flavonoids in vegetables, which scavenge free radicals and are strongly antioxidative, have been added to the list of protective compounds.^{24,25)}

A high intake of green-leafy vegetables, oranges and other fruits was, in our study, associated with a significant dose-dependent reduction in risk of lung cancer among males, and a high intake of the latter two was also associated among male current smokers. This result was consistent with numerous previous studies.^{1-7,14)} However, significantly low HRs were not observed for the highest intake of carrots and squash, and tomatoes. Exposure misclassification may be larger among males than females because males do not usually cook themselves and cannot

exactly evaluate their intake of those vegetables. In contrast, fruit consumption could be reported better, because fruits are eaten by choice. It was reported that the correlation between a food frequency questionnaire and four 4-day dietary records was better in females than in males for green-yellow vegetables and almost equal between the sexes for fruits.²⁶⁾ The comparison by sex was difficult in our validity data because most of the subjects were females.

Consumption of green-yellow vegetables has increased in Japan¹⁵⁾ and it may have reached a sufficient level to protect against carcinogenesis among most people. This cohort may be health-conscious and have consumed large amounts of green-yellow vegetables. In addition, people at a high health risk may increase their intake of green-yellow vegetables, because they have been promoted as being good for health. Those may be additional reasons why green-yellow vegetables did not show a clear protective effect.

Among females (also female nonsmokers), fruits and green-yellow vegetables were not associated with any reduction in risk of lung cancer. These results seemed to be inconsistent with the theory that high fruit or vegetable consumption reduces the risk of lung cancer. The exposure misclassification would tend to be smaller for females because they usually cook for themselves, so that it does not seem to have caused these obscure results. Intake of these foods did not seem to be strongly related to other diet risks. The possible reason is that the protection afforded by antioxidants and other protective agents may work less among nonsmokers because they have low oxidative stress and a smaller intake of carcinogenic agents. Some other studies showed similar results to our study.⁹⁻¹¹⁾

Among male ex-smokers, vegetables and fruits showed weaker protective effects than among current smokers. The reason may be that ex-smokers had less oxidative stress and smaller amounts of carcinogens derived from smoking because they quit smoking.

A high intake of cheese was associated with a reduction in the risk of lung cancer among all males and male ex-smokers. Some studies reported a risk reduction due to cheese and attributed it to the high vitamin A content.^{27, 28)} However, it has recently been thought that the protective effect of total dietary vitamin A may reflect the effect of carotenoids, rather than retinol itself.²⁾ Dairy foods are recognized as healthy in Japan, and the subjects interested in health checkup had a high intake of dairy foods in this study, so that high consumption of dairy foods may be related to underlying healthy lifestyle factors which reduce lung cancer risk in general.

It has been reported that high consumption of saturated fat and red meat increased the risk of lung cancer in analytical epidemiologic studies.^{3, 7)} Most studies showed a stronger association among men than women,¹⁾ but a study group showed an increased risk of lung cancer for a high total and saturated fat intake and red meat consumption among nonsmoking women, with a stronger association for adenocarcinoma.^{4, 12, 29)} Our study showed an increased risk of lung cancer for a high intake of ham and sausages, and liver. No decreased risks for a high intake of dairy foods were observed among females, despite the decreased risk among males. These results are partially consistent with the theories put forward in previous studies.

Associations of intake of ham and sausages, and liver with lung cancer deaths by sex were unclear. When the HRs for ham and sausages were additionally adjusted for cheese, green-leafy vegetables, and fruits other than oranges, the point estimate of HR for the highest intake compared with the lowest was still low among males (0.68, $P=0.14$). This hardly seems to suggest that the low HR was due to confounding by intake of dairy foods, vegetables, and fruits. Therefore, the result is still not explicable. On the other hand, the high HRs for a high intake of

ham and sausages, and liver among females were thought to reflect the association of fat-rich foods and adenocarcinoma. The association between dairy foods and potential healthy lifestyles may be cancelled from the viewpoint of fat intake, because dairy foods are rich in saturated fat and seem to be related to a Western-style diet, which is also richer in saturated fat than a Japanese-style diet.

A high intake of boiled rice in the 30s was positively associated with lung cancer death among male current smokers. Much consumption of boiled rice in the age of manhood may be associated with physical labor. This implies low socioeconomic status, which may be a potential risk factor. A high intake of miso-soup was also positively associated among females. Consumption of miso-soup seems to be associated with Japanese-style diet and increased salt intake. However, the significance of these findings is unclear.

In conclusion, in this large-scale cohort study in Japan, frequent vegetable and fruit consumption significantly decreased the risk of lung cancer death among males. This suggests that antioxidative micronutrients and anticarcinogenic agents rich in vegetables and fruits reduced oxidative stress and carcinogenesis due to smoking. Frequent intake of ham and sausages, and liver increased the risk among females, which is partially consistent with the hypothesis that high saturated fat consumption increases the risk of lung cancer, especially that of adenocarcinoma. Frequent intake of cheese may decrease the risk among males, but its consumption may reflect other concomitant healthy lifestyle factors.

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