

Risk of lung cancer and consumption of vegetables and fruit in Japanese: A pooled analysis of cohort studies in Japan

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International reviews have concluded that consumption of fruit and vegetables might decrease the risk of lung cancer. However, the relevant epidemiological evidence still remains insufficient in Japan. Therefore, we performed a pooled analysis of data from four population-based cohort studies in Japan with >200 000 participants and >1700 lung cancer cases. We computed study-specific hazard ratios by quintiles of vegetable and fruit consumption as assessed by food frequency questionnaires. Summary hazard ratios were estimated by pooling the study-specific hazard ratios with a fixed-effect model. In men, we found inverse associations between fruit consumption and the age-adjusted and area-adjusted risk of mortality or incidence of lung cancer. However, the associations were largely attenuated after adjustment for smoking and energy intake. The significant decrease in risk among men remained only for a moderate level of fruit consumption; the lowest summary hazard ratios were found in the third quintile of intake (mortality: 0.71, 95% confidence interval 0.60–0.84; incidence: 0.83, 95% confidence interval 0.70–0.98). This decrease in risk was mainly detected in ever smokers. Conversely, vegetable intake was positively correlated with the risk of incidence of lung cancer after adjustment for smoking and energy intake in men (trend *P*, 0.024); the summary hazard ratio for the highest quintile was 1.26 (95% confidence interval 1.05–1.50). However, a similar association was not detected for mortality from lung cancer. In conclusion, a moderate level of fruit consumption is associated with a decreased risk of lung cancer in men among the Japanese population.

The protective effects of vegetable and fruit consumption against the development of lung cancer have previously been examined in case-control and cohort studies.^(1,2) There has been particular interest in the potential of vegetables, which are rich in carotenoids, for reducing the risk of lung cancer. An international review by the World Cancer Research Fund and the American Institute for Cancer Research⁽²⁾ concluded that consumption of fruit and foods containing carotenoids probably decreases the risk of lung cancer, and that consumption of non-starchy vegetables possibly decreases this risk (the evidence was classified as “limited–suggestive”). This conclusion is in agreement with a review by the International Agency for Research on Can-

cer (IARC),⁽¹⁾ which reported that a high intake of fruit and vegetables is associated with a decreased risk of lung cancer, based on meta-analyses of cohort and case-control studies.

However, clinical trials of β -carotene supplementation failed to show a decrease in the risk of lung cancer.⁽³⁾ In addition, the hypothesized risk reduction in relation to the consumption of vegetables has been challenged in some recent large-scale prospective studies.⁽¹⁾

To establish cancer prevention strategies in Japan, re-assessment is required for the role of consumption of vegetables and fruit in the prevention of lung cancer. Our research group previously reviewed published epidemiological studies on the

Table 1. Characteristics of the four cohort studies in the pooled analysis of the association between consumption of fruit and vegetables and lung cancer risk

Study	Population	Age range at baseline (years)	Year of baseline survey	Population size	Response rate (%) for baseline questionnaire	Method of follow up	For present pooled analysis												
							For mortality				For incidence								
							Age range, year	Last follow up	Mean follow up period, year	Size of cohort	Number of cancer cases	Last follow up	Mean follow up period, year	Size of cohort	Number of cancer cases				
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women									
JPHC I	Japanese residents of 5 public health-center areas in Japan	40–59	1990	61 595	82	Cancer registry and death certificate	40–59	2008	17.8	20 178	21 657	262	66	2006	15.3	20 159	21 654	278	118
JPHC II	Japanese residents of 6 public health-center areas in Japan	40–69	1993–1994	78 825	80	Cancer registry and death certificate	40–69	2008	14.7	29 008	32 254	463	123	2006	12.1	28 978	32 241	503	152
JACC	Residents of 45 areas throughout Japan	40–79	1988–1990	110 792	83	Cancer registry (selected areas: 22) and death certificate	40–79	2008	15.8	23 815	36 434	543	179	2001	10.5	16 225	25 719	222	74
MIYAGI	Residents of 14 municipalities in Miyagi Prefecture, Japan	40–64	1990	47 605	92	Cancer registry and death certificate	40–64	2001	11.0	22 234	23 764	117	33	2003	12.8	22 208	23 756	297	98
Total										95 235	114 109	1385	401		87 570	103 370	1300	442	

JACC, The Japan Collaborative Cohort Study; JPHC, Japan Public Health Center-based Prospective Study; MIYAGI, The Miyagi Cohort Study.

association of vegetable and fruit consumption with the risk of lung cancer in the Japanese population.⁽⁴⁾ We showed that fruit consumption possibly decreases the risk of lung cancer in Japan, whereas there is insufficient epidemiological evidence for an association between vegetable consumption and the risk of lung cancer. This finding may indicate that a reduction in risk through the intake of vegetables and fruit, if any, is smaller in Japanese than in other populations.

However, in the process of this systematic review we realized that there is insufficient relevant evidence in Japan. To address this issue, we performed a pooled analysis of data from four large-scale cohort studies carried out in Japan with more than 200 000 participants.

Materials and Methods

Study populations. Since 2006, the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan has been conducting pooled analyses using original data from major cohort studies to examine the association of lifestyle factors with major cancers in Japanese people.^(5–10) The following inclusion criteria were defined *a priori* for the present analysis: (1) population-based cohort studies carried out in Japan; (2) studies initiated between the mid-1980s and mid-1990s; (3) involvement of more than 30 000 participants; (4) assessment of vegetable and fruit consumption in the baseline survey with a food frequency questionnaire (FFQ); and (5) follow up for the incidence and mortality of primary lung cancer as outcome information. We eventually identified

four studies that met these criteria: (1) the Japan Public Health Center-based Prospective Study-I (JPHC-I);⁽¹¹⁾ (2) the Japan Public Health Center-based Prospective Study-II (JPHC-II);⁽¹¹⁾ (3) the Japan Collaborative Cohort Study (JACC);⁽¹²⁾ and (4) the Miyagi Cohort Study (MIYAGI).⁽¹³⁾ Selected characteristics of these cohort studies are shown in Table 1.

We excluded data from participants with extreme energy intakes (>3 SD from the mean log_e-transformed energy intake in each study), those with missing information on dietary intake and those with a history of cancer at baseline. The relevant institutional review board approved each study. The JPHC-I and JPHC-II have already published results on the association of consumption of vegetables and fruit with the risk of lung cancer.⁽¹⁴⁾ In the current study, we reanalyzed the updated dataset for JPHC-I and JPHC-II.

Assessment of consumption of fruit and vegetables. In each study, dietary intake was assessed by means of self-administered FFQ. Although the FFQ differed by study, investigators in each cohort estimated the consumption in grams for the following food groups, based on the frequency of intake: (1) fruit; (2) total vegetables; (3) green-yellow vegetables; and (4) vegetables and fruit. The details of the questionnaires have been described previously.⁽¹⁵⁾ In brief, the questionnaire contained questions asking about the average frequency of intake of food items, including several vegetables and fruits. A portion size for each food item was determined in each cohort based on the median values observed in 12-day or 28-day dietary records (DR) that were collected in the validation studies for the FFQ.^(16–18) We computed daily intake of each food

Table 2. Summary hazard ratios for lung cancer mortality by level of consumption of vegetables and fruit

		Men				Women			
		Number of cases	Summary hazard ratio (95% CI)		Number of cases	Summary hazard ratio (95% CI)			
			Age and area-adjusted	Multivariate-adjusted†		Age and area-adjusted	Multivariate-adjusted†		
Fruit	Q1	344	1.00	1.00	90	1.00	1.00		
	Q2	261	0.74 (0.63–0.87)	0.80 (0.68–0.94)	74	0.85 (0.62–1.16)	0.91 (0.66–1.24)		
	Q3	231	0.64 (0.54–0.75)	0.71 (0.60–0.84)	77	0.89 (0.65–1.21)	0.98 (0.72–1.34)		
	Q4	271	0.71 (0.61–0.84)	0.85 (0.72–1.00)	77	0.88 (0.64–1.20)	0.97 (0.70–1.32)		
	Q5	278	0.71 (0.60–0.83)	0.90 (0.76–1.06)	83	0.94 (0.69–1.27)	1.03 (0.76–1.41)		
	Trend <i>P</i>			4×10^{-5}	0.275		0.805	0.700	
Vegetables and fruit	Q1	298	1.00	1.00	91	1.00	1.00		
	Q2	258	0.81 (0.69–0.96)	0.87 (0.74–1.03)	67	0.75 (0.55–1.04)	0.81 (0.59–1.11)		
	Q3	263	0.78 (0.66–0.93)	0.88 (0.75–1.04)	69	0.76 (0.56–1.05)	0.83 (0.60–1.14)		
	Q4	289	0.82 (0.69–0.96)	0.97 (0.82–1.14)	91	0.99 (0.74–1.33)	1.10 (0.82–1.49)		
	Q5	277	0.75 (0.64–0.89)	0.94 (0.79–1.11)	83	0.86 (0.63–1.16)	0.94 (0.69–1.27)		
	Trend <i>P</i>			0.003	0.890		0.890	0.659	
Green-yellow vegetables	Q1	279	1.00	1.00	77	1.00	1.00		
	Q2	265	0.92 (0.77–1.09)	0.98 (0.82–1.15)	76	1.01 (0.73–1.39)	1.06 (0.77–1.46)		
	Q3	255	0.84 (0.71–0.99)	0.92 (0.78–1.09)	81	1.02 (0.75–1.40)	1.10 (0.80–1.51)		
	Q4	286	0.87 (0.73–1.02)	0.98 (0.83–1.16)	78	0.94 (0.68–1.29)	1.01 (0.73–1.39)		
	Q5	300	0.82 (0.70–0.97)	0.99 (0.84–1.17)	89	1.01 (0.74–1.38)	1.10 (0.80–1.50)		
	Trend <i>P</i>			0.023	0.976		0.925	0.664	
Vegetables	Q1	258	1.00	1.00	79	1.00	1.00		
	Q2	265	0.98 (0.83–1.17)	1.04 (0.87–1.23)	82	1.05 (0.77–1.43)	1.11 (0.81–1.51)		
	Q3	263	0.91 (0.76–1.08)	0.98 (0.82–1.16)	71	0.89 (0.64–1.23)	0.93 (0.67–1.29)		
	Q4	292	0.97 (0.82–1.14)	1.05 (0.89–1.24)	81	0.96 (0.70–1.32)	1.02 (0.74–1.40)		
	Q5	307	0.96 (0.81–1.13)	1.09 (0.92–1.29)	88	0.98 (0.72–1.33)	1.03 (0.75–1.40)		
	Trend <i>P</i>			0.630	0.303		0.713	0.927	

†Adjusted for age, area, smoking and intake of total energy. CI, confidence interval; Q1–Q5, quintiles 1–5.

item by multiplying the portion size by intake frequency per day, and then estimated the consumption of fruit, total vegetables and green–yellow vegetables (g/day) by summing up the daily intake of food items belonging to each of the three food groups.

Correlation coefficients between intakes estimated from the questionnaires and those from DR for fruit, total vegetables and green–yellow vegetables, respectively, were 0.55, 0.27 and 0.25 in men and 0.35, 0.31 and 0.19 in women for the JPHC,⁽¹⁷⁾ and 0.76, 0.60 and 0.54 in men and 0.70, 0.45 and 0.44 in women for the MIYAGI.⁽¹⁶⁾ Although the validity for vegetable and fruit intake as food groups was not reported in the JACC FFQ, the same questions posed in the MIYAGI were asked regarding intake. Furthermore, Spearman's rank correlation coefficients between intake frequencies from the JACC FFQ and those from DR for each food item of fruit and vegetables were reasonably high for individual foods (range, 0.18–0.45; median, 0.33).⁽¹⁸⁾ Smoking habits were determined using the baseline questionnaires. Based on responses to the questionnaires, never smokers were defined as follows: participants who answered no to the question “Have you ever been a smoker?” in the JPHC-I; those who answered no to the question “Do you currently smoke cigarettes?” and did not respond to any question for former smokers (age at quitting smoking, number of cigarettes smoked per day and age at starting smoking) in the JPHC-II; and those who chose the last response from the three possible responses, namely, “I smoke,” “I used to smoke, but I quit” and “I have not smoked” in the JACC and MIYAGI.

Follow up and study outcome. Participants were followed from the baseline survey until the last date of follow up in each study (Table 1). Vital status was confirmed through the residential registry. Information on the cause of death was obtained from death certificates, and the cause of death was coded according to the International Classification of Diseases, Tenth Revision (ICD-10). Information on diagnosis of cancer was collected for the whole population in the JPHC-I, JPHC-II and MIYAGI through active patient notification from major local hospitals and/or population-based cancer registries. In the JACC, information on diagnosis of cancer was collected in 22 out of 45 study areas. Cancer cases were coded using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3). The study outcome was defined as death or incidence of lung cancer (ICD-10, code C34 or ICD-O-3, topography code C34). The percentage of incident cases microscopically verified was 87.3% in the JPHC-I, 80.5% in the JPHC-II and 86.5% in the MIYAGI. The percentage could not be calculated in the JACC because the information on diagnostic method was unavailable for 64% of lung cancer cases in the cohort.

Statistical analyses. Analysis of the data included two parts: analyses for mortality from lung cancer and the incidence of lung cancer. The follow-up period was calculated from the date of the baseline survey in each study until the date of death or diagnosis of lung cancer, migration from the study area or emigration from Japan (for the analyses of mortality in the JPHC-I and JPHC-II), death from any cause or the end of follow up, whichever came first. Losses to follow up due to

Table 3. Summary hazard ratios for lung cancer mortality by level of consumption of vegetables and fruit among never smokers

	Men		Women					
			Number of cases	Summary hazard ratio (95% CI)		Number of cases	Summary hazard ratio (95% CI)	
				Age and area-adjusted	Multivariate-adjusted†		Age and area-adjusted	Multivariate-adjusted†
Fruit	Q1	96	1.00	1.00	62	1.00	1.00	
	Q2	97	1.14 (0.53–2.45)	1.11 (0.51–2.40)	50	0.79 (0.54–1.16)	0.79 (0.54–1.15)	
	Q3	81	0.89 (0.41–1.96)	0.90 (0.41–1.97)	66	1.09 (0.77–1.55)	1.08 (0.76–1.53)	
	Q4	89	0.88 (0.40–1.92)	0.89 (0.41–1.94)	69	1.11 (0.78–1.57)	1.09 (0.77–1.55)	
	Q5	112	1.00 (0.47–2.15)	1.00 (0.47–2.16)	64	1.05 (0.73–1.50)	1.05 (0.74–1.51)	
	Trend <i>P</i>		0.737	0.748		0.252	0.248	
Vegetables and fruit	Q1	91	1.00	1.00	60	1.00	1.00	
	Q2	91	1.00 (0.48–2.09)	1.01 (0.48–2.11)	51	0.91 (0.63–1.33)	0.91 (0.62–1.33)	
	Q3	80	0.35 (0.13–0.92)	0.35 (0.13–0.93)	57	1.03 (0.71–1.49)	1.02 (0.70–1.48)	
	Q4	108	0.91 (0.44–1.87)	0.93 (0.45–1.91)	81	1.37 (0.97–1.93)	1.36 (0.96–1.92)	
	Q5	105	0.74 (0.36–1.52)	0.74 (0.36–1.53)	62	1.00 (0.69–1.44)	1.00 (0.69–1.44)	
	Trend <i>P</i>		0.980	0.998		0.312	0.319	
Green–yellow vegetables	Q1	90	1.00	1.00	52	1.00	1.00	
	Q2	82	1.33 (0.56–3.19)	1.36 (0.57–3.26)	63	1.30 (0.89–1.88)	1.29 (0.89–1.88)	
	Q3	101	1.06 (0.43–2.63)	1.10 (0.44–2.72)	66	1.25 (0.86–1.81)	1.23 (0.85–1.80)	
	Q4	101	1.51 (0.68–3.39)	1.57 (0.70–3.52)	57	1.08 (0.74–1.59)	1.07 (0.73–1.58)	
	Q5	101	1.11 (0.49–2.54)	1.12 (0.49–2.54)	73	1.27 (0.88–1.84)	1.27 (0.88–1.84)	
	Trend <i>P</i>		0.690	0.678		0.491	0.505	
Vegetables	Q1	88	1.00	1.00	55	1.00	1.00	
	Q2	91	0.88 (0.41–1.92)	0.90 (0.41–1.95)	67	1.23 (0.86–1.77)	1.23 (0.85–1.76)	
	Q3	91	1.06 (0.51–2.21)	1.08 (0.52–2.25)	55	1.00 (0.69–1.46)	0.99 (0.68–1.45)	
	Q4	97	0.58 (0.24–1.37)	0.59 (0.25–1.40)	66	1.11 (0.77–1.59)	1.10 (0.76–1.58)	
	Q5	108	0.97 (0.49–1.90)	0.96 (0.49–1.89)	68	1.08 (0.75–1.55)	1.08 (0.75–1.55)	
	Trend <i>P</i>		0.681	0.651		0.950	0.961	

†Adjusted for age, area and intake of total energy. CI, confidence interval; Q1–Q5, quintiles 1–5.

Table 4. Summary hazard ratios for lung cancer mortality by level of consumption of vegetables and fruit among ever smokers

		Men			Women		
		Number of cases	Summary hazard ratio (95% CI)		Number of cases	Summary hazard ratio (95% CI)	
			Age and area-adjusted	Multivariate-adjusted†		Age and area-adjusted	Multivariate-adjusted†
Fruit	Q1	308	1.00	1.00	19	1.00	1.00
	Q2	247	0.77 (0.65–0.91)	0.81 (0.68–0.95)	20	1.28 (0.71–2.31)	1.36 (0.75–2.48)
	Q3	210	0.64 (0.53–0.76)	0.69 (0.58–0.82)	11	0.48 (0.20–1.14)	0.53 (0.22–1.25)
	Q4	252	0.76 (0.64–0.90)	0.85 (0.72–1.01)	11	0.44 (0.18–1.07)	0.51 (0.21–1.26)
	Q5	266	0.75 (0.63–0.88)	0.87 (0.74–1.04)	9	0.56 (0.25–1.27)	0.58 (0.25–1.32)
	Trend <i>P</i>		0.001	0.177		0.031	0.049
Vegetables and fruit	Q1	262	1.00	1.00	23	1.00	1.00
	Q2	239	0.82 (0.69–0.98)	0.86 (0.72–1.02)	16	0.62 (0.32–1.18)	0.61 (0.32–1.18)
	Q3	244	0.82 (0.69–0.98)	0.89 (0.75–1.05)	10	0.25 (0.10–0.65)	0.27 (0.10–0.71)
	Q4	277	0.88 (0.74–1.04)	0.99 (0.83–1.17)	8	0.41 (0.17–0.95)	0.47 (0.20–1.10)
	Q5	261	0.80 (0.67–0.95)	0.93 (0.78–1.10)	13	0.57 (0.29–1.13)	0.61 (0.31–1.22)
	Trend <i>P</i>		0.056	0.963		0.015	0.035
Green–yellow vegetables	Q1	259	1.00	1.00	17	1.00	1.00
	Q2	232	0.88 (0.74–1.05)	0.91 (0.77–1.09)	14	0.62 (0.29–1.32)	0.67 (0.32–1.45)
	Q3	239	0.85 (0.72–1.02)	0.92 (0.77–1.10)	10	0.69 (0.32–1.48)	0.76 (0.36–1.64)
	Q4	263	0.85 (0.71–1.01)	0.92 (0.77–1.10)	15	0.61 (0.29–1.28)	0.71 (0.33–1.50)
	Q5	290	0.85 (0.72–1.01)	0.97 (0.82–1.15)	14	0.57 (0.27–1.18)	0.64 (0.31–1.33)
	Trend <i>P</i>		0.071	0.799		0.206	0.326
Vegetables	Q1	234	1.00	1.00	18	1.00	1.00
	Q2	247	0.99 (0.83–1.18)	1.03 (0.86–1.23)	16	0.88 (0.45–1.73)	0.95 (0.48–1.86)
	Q3	243	0.92 (0.77–1.11)	0.97 (0.81–1.17)	12	0.57 (0.26–1.26)	0.63 (0.29–1.40)
	Q4	272	0.98 (0.82–1.17)	1.04 (0.87–1.24)	10	0.46 (0.20–1.06)	0.50 (0.22–1.17)
	Q5	287	0.99 (0.83–1.18)	1.09 (0.92–1.30)	14	0.69 (0.35–1.39)	0.77 (0.39–1.56)
	Trend <i>P</i>		0.855	0.383		0.103	0.192

†Adjusted for age, area, smoking and intake of total energy. CI, confidence interval; Q1–Q5, quintiles 1–5.

migration and deaths not due to lung cancer were treated as censored cases by using proportional hazards models in the analyses of both mortality and incidence. The diagnosis of cancers other than malignant lung tumors was not treated as an end of follow up. To minimize the effects of malignancy itself, the first 3 years from baseline were excluded from the risk period.

For inclusion in estimation of summary statistics, we conducted study-specific analysis stratified by sex. Each analysis used a proportional hazards model to estimate the hazard ratios (HR) and their 95% confidence intervals (CI) for the mortality or incidence of lung cancer by consumption level of the four groups of fruit and vegetables (fruit, vegetables and fruit, green–yellow vegetables, and vegetables). The consumption was adjusted for total energy intake by the residual method⁽¹⁹⁾ and was categorized into quintiles. We used sex-specific and cohort-specific cutoff points for the quintiles (Suppl. Table S1). The HR were computed for the second to the highest quintiles versus the lowest. All of the studies estimated two types of HR: age- (continuous) and area-adjusted (within each study for JPHC-I, JPHC-II and JACC) HR and multivariate-adjusted HR. The multivariate model included smoking (never smokers, ex-smokers who had quit smoking <5, 5–9, 10–14, 15–19 or 20+ years ago; current smokers with <20, 20–39, 40–59, 60–79, 80–99 or 100+ pack-years; and unknown) and intake of total energy (continuous) in addition to age and area. Pack-years in current smokers were calculated as (daily consumption of tobacco [number of cigarettes/day]) × (duration of smoking [years])

/20. We incorporated total energy intake because its inclusion may reduce the random error in the effect of vegetable/fruit intake if energy intake has an important association with the outcome.⁽¹⁹⁾ We also conducted subgroup analyses in never smokers and ever smokers (ex-smokers and current smokers), whereby we determined sex-specific and cohort-specific cutoff points for quintiles of vegetable and fruit intakes separately for the two subgroups. SAS version 9.1 (SAS Institute, Cary, NC, USA) or STATA, version 10.1 (Stata Corporation, College Station, TX, USA) statistical software was used for these estimations.

To obtain a single pooled estimate of the HR from the individual studies for each quintile, we applied a fixed-effect model. The pooled HR was statistically tested individually for the second to the highest quintiles versus the lowest; the null hypothesis was that the risk of lung cancer mortality or incidence was not different between individuals with each of the second to the highest quintile of vegetable/fruit intakes and those with the lowest quintile. We did not consider possible issues of multiple comparisons, as in the previous analysis regarding the risk of stomach cancer and consumption of vegetables and fruit.⁽¹⁵⁾ We tested heterogeneity among studies for each category by using Cochran's Q statistic and found no apparent indication of heterogeneity ($P > 0.05$ for all categories). The dose-response relationship was examined by models in which the lowest to the top quintiles were scored as 0, 1, 2, 3 and 4, respectively, and were incorporated as explanatory variables in individual studies. Resultant HR from all of the four cohorts were combined

using a fixed-effect model. The “metan” command (<http://www.stata.com/stb/stb44>) for STATA was used for the present meta-analysis.

Results

With regard to lung cancer mortality, we found significant inverse associations of consumption of fruit, vegetables and fruit, and green–yellow vegetables with age-adjusted and area-adjusted risk in men (Table 2). However, adjustment for smoking and total energy intake largely weakened the association; a significantly decreased risk was observed only in the second and third quintiles of consumption for fruit. The lowest summary HR was found in the third quintile (0.71; 95% CI 0.60–0.84; $P = 6 \times 10^{-5}$). When the study population was stratified by smoking habits, the decreased risk associated with fruit consumption was observed only among ever smokers (Tables 3 and 4). For female ever smokers, we found a somewhat inverse association of consumption of fruit, or vegetables and fruit, with a risk for mortality, although the number of fatal lung cancer cases was small ($n = 70$, Table 4).

With regard to the incidence of lung cancer (Tables 5–7), significant inverse associations between consumption of fruit and vegetables and the multivariate-adjusted risk were only detected in the third quintile of fruit consumption in all men (summary HR, 0.83; 95% CI 0.70–0.98; $P = 0.032$; Table 5) and male ever smokers (summary HR, 0.83; 95% CI 0.69–0.99; Table 7), and in the third quintile of fruit and vegetable

consumption in male never smokers (summary HR, 0.41; 95% CI 0.18–0.91; Table 6). The decrease in risk of incidence of lung cancer was generally smaller compared with that for mortality from lung cancer. In contrast, a significantly increased risk for the incidence of lung cancer was correlated with a higher intake of vegetables among all men and men who were ever smokers. The summary HR for the highest quintile was 1.26 (95% CI 1.05–1.50) for all men (Table 5) and 1.28 (95% CI 1.06–1.54) for men who were ever smokers (Table 7).

For never smokers, we also analyzed the data after combining men and women (Tables S2 and S3). The findings were essentially similar to those of the analyses stratified by sex.

Discussion

In the present pooled analysis, we found inverse associations between fruit consumption and the age-adjusted and area-adjusted risk of mortality or incidence of lung cancer in men. The risk of mortality was also negatively correlated with consumption of green–yellow vegetables. However, these associations were largely attenuated after adjustment for smoking and intake of total energy. The significant decrease in the risk of mortality or incidence of lung cancer in men only remained for a moderate level of fruit intake (around median intake). This decrease in risk was mainly detected in ever smokers. In contrast, vegetable intake was positively correlated with the risk of incidence of lung cancer after adjustment for smoking and energy intake.

Table 5. Summary hazard ratios for lung cancer incidence by level of consumption of vegetables and fruit

	Number of cases		Men		Number of cases		Women	
			Summary hazard ratio (95% CI)				Summary hazard ratio (95% CI)	
			Age and area-adjusted	Multivariate-adjusted†			Age and area-adjusted	Multivariate-adjusted†
Fruit	Q1	301	1.00	1.00	90	1.00	1.00	
	Q2	254	0.83 (0.70–0.98)	0.89 (0.75–1.06)	87	0.98 (0.73–1.31)	1.02 (0.75–1.37)	
	Q3	233	0.75 (0.63–0.89)	0.83 (0.70–0.98)	96	1.06 (0.79–1.43)	1.13 (0.84–1.52)	
	Q4	248	0.76 (0.64–0.90)	0.89 (0.75–1.05)	78	0.84 (0.62–1.15)	0.89 (0.65–1.22)	
	Q5	264	0.77 (0.65–0.91)	0.96 (0.81–1.14)	91	0.99 (0.74–1.34)	1.04 (0.77–1.41)	
	Trend <i>P</i>		0.001	0.589		0.714	0.944	
Vegetables and fruit	Q1	253	1.00	1.00	86	1.00	1.00	
	Q2	264	1.00 (0.84–1.19)	1.07 (0.90–1.28)	92	1.07 (0.79–1.44)	1.11 (0.82–1.49)	
	Q3	237	0.85 (0.71–1.02)	0.95 (0.79–1.14)	80	0.90 (0.66–1.23)	0.94 (0.69–1.28)	
	Q4	278	0.95 (0.80–1.12)	1.12 (0.94–1.33)	92	1.01 (0.75–1.37)	1.07 (0.80–1.45)	
	Q5	268	0.88 (0.74–1.05)	1.07 (0.90–1.28)	92	1.00 (0.74–1.35)	1.04 (0.77–1.41)	
	Trend <i>P</i>		0.123	0.354		0.897	0.866	
Green–yellow vegetables	Q1	253	1.00	1.00	83	1.00	1.00	
	Q2	235	0.92 (0.77–1.10)	0.98 (0.82–1.18)	81	1.00 (0.74–1.37)	1.04 (0.76–1.41)	
	Q3	244	0.91 (0.77–1.09)	1.00 (0.84–1.19)	94	1.13 (0.84–1.52)	1.17 (0.87–1.58)	
	Q4	279	0.97 (0.82–1.15)	1.09 (0.92–1.29)	81	0.94 (0.69–1.28)	0.98 (0.72–1.34)	
	Q5	289	0.93 (0.78–1.10)	1.10 (0.93–1.31)	103	1.15 (0.85–1.54)	1.20 (0.89–1.61)	
	Trend <i>P</i>		0.645	0.122		0.497	0.323	
Vegetables	Q1	221	1.00	1.00	74	1.00	1.00	
	Q2	243	1.07 (0.89–1.29)	1.14 (0.95–1.37)	109	1.46 (1.09–1.97)	1.50 (1.12–2.02)	
	Q3	275	1.13 (0.95–1.35)	1.21 (1.01–1.45)	77	1.00 (0.72–1.38)	1.03 (0.75–1.42)	
	Q4	266	1.05 (0.88–1.26)	1.14 (0.95–1.37)	83	1.04 (0.75–1.42)	1.07 (0.78–1.47)	
	Q5	295	1.11 (0.93–1.33)	1.26 (1.05–1.50)	99	1.19 (0.88–1.61)	1.22 (0.90–1.65)	
	Trend <i>P</i>		0.335	0.024		0.941	0.955	

†Adjusted for age, area, smoking and intake of total energy. CI, confidence interval; Q1–Q5, quintiles 1–5.

Table 6. Summary hazard ratios for lung cancer incidence by level of consumption of vegetables and fruit among never smokers

		Number of cases	Men		Number of cases	Women	
			Summary hazard ratio (95% CI)			Summary hazard ratio (95% CI)	
			Age and area-adjusted	Multivariate-adjusted†		Age and area-adjusted	Multivariate-adjusted†
Fruit	Q1	21	1.00	1.00	69	1.00	1.00
	Q2	14	0.86 (0.42–1.77)	0.80 (0.39–1.65)	61	0.86 (0.60–1.22)	0.86 (0.60–1.22)
	Q3	17	0.79 (0.37–1.66)	0.78 (0.37–1.65)	78	1.09 (0.78–1.52)	1.09 (0.78–1.53)
	Q4	19	0.64 (0.30–1.35)	0.66 (0.31–1.40)	67	0.91 (0.64–1.29)	0.90 (0.64–1.28)
	Q5	15	0.73 (0.35–1.51)	0.69 (0.33–1.44)	74	1.03 (0.73–1.44)	1.02 (0.73–1.44)
	Trend <i>P</i>		0.720	0.692		0.559	0.600
Vegetables and fruit	Q1	22	1.00	1.00	59	1.00	1.00
	Q2	16	0.68 (0.34–1.37)	0.72 (0.36–1.46)	76	1.21 (0.85–1.72)	1.21 (0.85–1.72)
	Q3	11	0.39 (0.18–0.87)	0.41 (0.18–0.91)	62	1.10 (0.77–1.57)	1.10 (0.77–1.57)
	Q4	19	0.57 (0.28–1.20)	0.59 (0.28–1.24)	76	1.20 (0.84–1.70)	1.19 (0.84–1.69)
	Q5	18	0.67 (0.34–1.30)	0.67 (0.34–1.30)	76	1.19 (0.84–1.69)	1.19 (0.84–1.68)
	Trend <i>P</i>		0.575	0.523		0.404	0.430
Green–yellow vegetables	Q1	12	1.00	1.00	57	1.00	1.00
	Q2	21	1.74 (0.80–3.81)	1.85 (0.84–4.06)	74	1.20 (0.84–1.72)	1.21 (0.85–1.73)
	Q3	14	1.19 (0.51–2.79)	1.29 (0.55–3.02)	73	1.31 (0.92–1.85)	1.30 (0.92–1.84)
	Q4	18	1.40 (0.61–3.21)	1.53 (0.66–3.52)	59	0.97 (0.67–1.41)	0.98 (0.68–1.42)
	Q5	21	1.57 (0.74–3.33)	1.62 (0.76–3.44)	86	1.33 (0.95–1.88)	1.34 (0.95–1.88)
	Trend <i>P</i>		0.646	0.606		0.275	0.273
Vegetables	Q1	17	1.00	1.00	54	1.00	1.00
	Q2	15	0.74 (0.32–1.73)	0.80 (0.34–1.87)	86	1.64 (1.16–2.32)	1.64 (1.16–2.32)
	Q3	18	1.05 (0.53–2.07)	1.12 (0.56–2.20)	60	1.10 (0.76–1.61)	1.11 (0.76–1.61)
	Q4	16	0.66 (0.31–1.42)	0.69 (0.32–1.49)	70	1.20 (0.84–1.73)	1.20 (0.84–1.73)
	Q5	20	0.97 (0.49–1.90)	0.96 (0.49–1.89)	79	1.35 (0.94–1.92)	1.34 (0.94–1.91)
	Trend <i>P</i>		0.985	0.911		0.692	0.719

†Adjusted for age, area and intake of total energy. CI, confidence interval; Q1–Q5, quintiles 1–5.

The present finding that the potential protective effect on lung cancer is more evident for fruit consumption than for vegetable intake is in line with that of the international review by the World Cancer Research Fund and the American Institute for Cancer Research,⁽²⁾ and that of the review for the Japanese population by our research group.⁽⁴⁾ However, the inverse association of fruit consumption with the risk of mortality or incidence of lung cancer was less clear in the present pooled analysis compared with the previous review by our group. The trend in risk with increasing fruit intake was not statistically significant in the current study, while the summary relative risk per serving per day of fruit consumption was significantly smaller than unity (0.92; 95% CI 0.84–1.00) in the systematic review for Japanese people.⁽⁴⁾

Residual confounding effects attributable to smoking might have resulted in overestimation of the decrease in risk of mortality or incidence of lung cancer in our previous review. Strata broader than used in the present pooled analysis were used to adjust for smoking habits in several previous studies, as we pointed out in that review.⁽⁴⁾ In the current study, consideration of smoking as a confounding factor greatly attenuated the apparent correlation of consumption of fruit and green–yellow vegetables with the decrease in risk, which suggests substantial residual confounding in some previous studies. In addition, because the lowest HR was found in the third quintile of fruit consumption in our study, some of the participants would have consumed more fruit than the optimal level to prevent lung cancer.

The evidence for a reduction in risk associated with consumption of vegetables and fruit has often been derived from

case-control studies.^(1,2,4) However, these studies might have overestimated the reduction compared with cohort studies, which has been suggested in international reviews.^(1,2) This overestimation could be ascribable to recall bias in the assessment of dietary intake.

Because the present study was conducted among Japanese, consumption levels and types of vegetables and fruit, as well as biological characteristics of lung cancer, may differ from those in other populations. Matsuo *et al.*⁽²⁰⁾ showed that the risk of lung cancer in individuals without epidermal growth factor receptor mutation was more inversely correlated with the intake of green–yellow vegetables and fruit compared with persons with this mutation. Because epidermal growth factor receptor mutation is more frequently found in lung cancer among East Asians, including Japanese,^(21,22) than in Western populations, protective effects of green–yellow vegetables and fruit, if any, might be smaller in Japan.

In our study, the significantly lower summary HR in relation to moderate fruit consumption was found only in men. This finding may be explained by the higher proportion of ever smokers in men than in women (78 versus 8% in the analysis for mortality and incidence) because such a decrease in risk was only found in ever smokers. This result may be in line with those of case-control studies reviewed by the IARC.⁽¹⁾ In addition, a reduction in risk of death from lung cancer, which was associated with higher concentrations of serum carotenoids, was stronger in current smokers than in never or former smokers in a cohort study.⁽²³⁾

Surprisingly, we found an upward trend in the risk of incidence of lung cancer with an increasing intake of vegetables.

Table 7. Summary hazard ratios for lung cancer incidence by level of consumption of vegetables and fruit among ever smokers

		Men				Women			
		Number of cases	Summary hazard ratio (95% CI)		Number of cases	Summary hazard ratio (95% CI)			
			Age and area-adjusted	Multivariate-adjusted†		Age and area-adjusted	Multivariate-adjusted†		
Fruit	Q1	265	1.00	1.00	10	1.00	1.00		
	Q2	232	0.86 (0.72–1.02)	0.90 (0.76–1.08)	21	2.00 (1.02–3.90)	2.06 (1.05–4.04)		
	Q3	219	0.77 (0.64–0.92)	0.83 (0.69–0.99)	8	1.31 (0.55–3.14)	1.37 (0.57–3.28)		
	Q4	224	0.81 (0.68–0.97)	0.90 (0.76–1.08)	14	1.01 (0.41–2.52)	1.05 (0.42–2.64)		
	Q5	256	0.83 (0.70–0.99)	0.97 (0.81–1.16)	8	0.81 (0.31–2.08)	0.79 (0.30–2.06)		
	Trend <i>P</i>		0.028	0.648		0.420	0.464		
Vegetables and fruit	Q1	223	1.00	1.00	15	1.00	1.00		
	Q2	236	1.01 (0.84–1.21)	1.05 (0.88–1.26)	16	0.92 (0.46–1.86)	0.93 (0.46–1.88)		
	Q3	222	0.91 (0.75–1.09)	0.97 (0.81–1.17)	8	0.46 (0.18–1.21)	0.47 (0.18–1.24)		
	Q4	261	1.02 (0.85–1.22)	1.13 (0.95–1.36)	14	1.12 (0.54–2.36)	1.24 (0.59–2.63)		
	Q5	254	0.95 (0.79–1.13)	1.08 (0.90–1.30)	8	0.54 (0.23–1.26)	0.56 (0.24–1.30)		
	Trend <i>P</i>		0.602	0.282		0.149	0.201		
Green–yellow vegetables	Q1	233	1.00	1.00	13	1.00	1.00		
	Q2	209	0.89 (0.74–1.07)	0.93 (0.77–1.12)	12	0.75 (0.32–1.73)	0.79 (0.34–1.83)		
	Q3	215	0.90 (0.75–1.08)	0.96 (0.80–1.16)	9	1.15 (0.45–2.95)	1.20 (0.46–3.08)		
	Q4	268	0.99 (0.83–1.19)	1.07 (0.90–1.28)	15	1.08 (0.51–2.28)	1.14 (0.53–2.41)		
	Q5	271	0.94 (0.78–1.12)	1.06 (0.89–1.27)	12	0.75 (0.33–1.70)	0.78 (0.34–1.78)		
	Trend <i>P</i>		0.927	0.209		0.658	0.702		
Vegetables	Q1	195	1.00	1.00	14	1.00	1.00		
	Q2	235	1.14 (0.94–1.37)	1.18 (0.98–1.43)	16	1.16 (0.57–2.37)	1.22 (0.60–2.49)		
	Q3	247	1.15 (0.95–1.38)	1.20 (0.99–1.45)	10	0.75 (0.32–1.78)	0.76 (0.32–1.82)		
	Q4	244	1.10 (0.91–1.32)	1.15 (0.96–1.39)	9	0.90 (0.36–2.26)	0.95 (0.38–2.39)		
	Q5	275	1.18 (0.98–1.41)	1.28 (1.06–1.54)	12	0.82 (0.38–1.75)	0.86 (0.40–1.85)		
	Trend <i>P</i>		0.229	0.039		0.242	0.285		

†Adjusted for age, area, smoking and intake of total energy. CI, confidence interval; Q1–Q5, quintiles 1–5.

This finding may have been the result of chance, as a similar association was not detected for mortality from lung cancer. Nevertheless, unknown confounding factors that are correlated with vegetable consumption cannot be ruled out. A possible reason to explain the positive correlation of intake of vegetables with the incidence of lung cancer may be that latent lung cancers are detected among participants in screening, and their incidence is seemingly increased among them. This might result in a positive correlation between vegetable intake and the incidence of lung cancer because participants in cancer screening programs are generally health-conscious and likely to consume more vegetables.⁽²⁴⁾

The strengths of the current study include its prospective design, population-based settings, long follow up, and adjustments with detailed strata for smoking, which is the strongest confounder next to age. The pooling of data from cohort studies enabled us to determine the risk of lung cancer associated with consumption of vegetables and fruit in a large sample size using common statistical procedures.

Some methodological limitations of our study warrant discussion. First, although the FFQ used in each cohort was validated by referring to DR, the number of vegetables or fruits was relatively small in most cases to cover their consumption. Generally, the assessment of vegetable consumption with an FFQ will be difficult compared with fruit intake,⁽²⁵⁾ as was the case in the present study. The association of vegetable consumption with the risk of lung cancer might have been attenuated because of error in the estimate of intake.⁽²⁶⁾ Second, we

did not examine the risk by histological type because this information was not available for a considerable proportion of lung cancer cases, particularly in the JACC Study, and the pooled data by histological classification from the JPHC-I and JPHC-II had already been published.⁽¹⁴⁾ Third, the follow up was continued after the diagnosis of cancers other than malignant lung tumors, so that some cases of metastatic tumors in the lung might have been erroneously included as incident cases of lung cancer. In addition, we did not consider possible issues of multiple comparisons. Although this may be a routine procedure in the analysis of dose-response relationships,⁽¹⁵⁾ some of the marginally significant summary HR should be interpreted with caution. Finally, dietary intake was assessed only once at baseline.

In conclusion, a moderate level of fruit consumption is associated with a decreased risk of lung cancer in men in the Japanese population, particularly in ever smokers.

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Disclosure Statement

The authors have no conflicts of interest.

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Appendix 1
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Supporting Information

Additional supporting information may be found in the online version of this article:

Table S1. Cutoff points used for quintiles of vegetable and fruit intakes by sex and cohort.

Table S2. Summary hazard ratios for lung cancer mortality by level of consumption of vegetables and fruit among never smokers (men and women combined).

Table S3. Summary hazard ratios for lung cancer incidence by level of consumption of vegetables and fruit among never smokers (men and women combined).