Table 2. *Continued*

Reference	Study period	Study subjects				Food item	Category	Odds ratios (95% CI or *P*)	*P* for trend	Confounding variables considered
		Type and source	Definition	Number of cases	Number of controls					
							5/week+	1.37 (0.46–4.09)		
						Carrots	<1/week	1.00	0.08	
							1–2/week	1.05 (0.46–2.41)		
							3–4/week	0.51 (0.19–1.40)		
							5/week+	0.47 (0.16–1.43)		
						Pumpkin	<1/week	1.00	0.82	
							1–2/week	0.81 (0.40–1.63)		
							3–4/week	0.78 (0.30–2.01)		
							5/week+	1.18 (0.32–4.30)		
						Fruit	Almost never	1.00	0.67	
							Occasionally	0.50 (0.11–2.31)		
							3–4/week	0.34 (0.07–1.60)		
							Every day	0.49 (0.11–2.13)		
Matsuo et al. (18)	2001–2005	Hospital-based (Aichi Cancer Center)	Cases: histologically diagnosed non-small-cell lung cancer cases. Controls: first-visit to outpatients without cancer.	122 female and male cases of lung cancer with *EGFR* mutation	1757 men and women	Green-yellow vegetables	T1	1.00	0.28	Age, sex, energy intake and smoking
							T2	1.06 (0.64–1.74)		
							T3	0.76 (0.45–1.29)		
						Other vegetables	T1	1.00	0.53	
							T2	0.81 (0.49–1.33)		
							T3	0.84 (0.51–1.37)		
						Fruit	T1	1.00	0.60	
							T2	0.93 (0.55–1.56)		
							T3	1.10 (0.66–1.85)		
				231 male and female cases of lung cancer without *EGFR* mutation	1757 men and women	Green-yellow vegetables	T1	1.00	0.044	
							T2	0.78 (0.56–1.10)		

	T3	0.69 (0.47–1.00)			
Other vegetables	T1	1.00	0.16		
	T2	0.72 (0.51–1.02)			
	T3	0.78 (0.53–1.11)			
Fruit	T1	1.00	0.096		
	T2	0.91 (0.65–1.27)			
	T3	0.72 (0.49–1.06)			

CI, confidence interval; NS, not significant; SQ, squamous cell carcinoma; AD, adenocarcinoma; SM, small cell carcinoma; *EGFR*, epidermal growth factor receptor; T1–T3, tertiles 1–3

for the highest intake category (versus the lowest) was statistically significant, or if the *P*-value for the trend was <0.05. If the trend *P* value was not available in an article, it was estimated from the HRs or ORs along with their 95% CIs by food-intake category. More specifically, the $\log_e$(HR) or $\log_e$(OR) was regressed on the intake score with the reciprocal of variance of the $\log_e$(HR) or $\log_e$(OR) in each intake category, derived from the CIs, used for weighting. The regression model was linear without an intercept, and the *P* value for its slope was considered as the trend *P* value. An intake score of 0, 1, 2, etc. was assigned from the lowest intake category through to the highest group. This estimate was also made with the STATA statistical package.

Meta-Analysis of Lung Cancer Risk and Fruit Consumption

Because inverse associations between lung cancer risk and fruit consumption were found across several cohort and case–control studies, we conducted a meta-analysis to investigate further. We used two types of analysis to estimate the summary relative risk (RR) for the highest versus lowest intake category and that per serving per day. The method described in the section on the 'Evaluation of results from individual studies' was used for the meta-analysis.

In the analysis of RR per serving per day, one serving was assumed to correspond to 80 g consumption, as in the review by the World Cancer Research Fund and the American Institute for Cancer Research (2). For each individual study, a variance-weighted log-linear regression analysis of the HRs or ORs was performed according to the mean, median or midpoint of fruit consumption, except in the case of studies that included only two exposure categories, for which the value of the logarithm of the HRs or ORs for one serving was used (8). The resultant figures per serving per day from individual studies were then synthesized to obtain the summary measure. To validate the results, we also made a sensitivity analysis using 70, 80, 90 and 100 g for one serving of fruit.

Overall Judgement on Strength of Evidence

The strength of the evidence was then evaluated by applying a method similar to that used in the World Health Organisation (WHO)/Food and Agriculture Organisation (FAO) Expert Consultation Report (9), in which evidence was classified as 'convincing', 'probable', 'possible' or 'insufficient'. We assumed that the biological plausibility, based on the evidence from experimental animals and mechanistic or other relevant data, corresponded to the judgment of the most recent evaluation from the IARC (1). Despite the use of this quantitative assessment procedure, an arbitrary assessment could not be avoided in cases where considerable variation existed in the magnitude of the associations reported between the results of different studies. Our final judgment was made based on a consensus of the

Table 3. Summary of associations between lung cancer risk and consumption of vegetables and fruit in cohort studies of Japanese populations

Reference	Study period	Study subjects					Green-yellow vegetables				Fruit			
		Sex	Number of subjects	Age (years)	Event	Number of incident cases or deaths	Magnitude of association[a]	HR (95% CI)	Intake categories	Trend *P*	Magnitude of association[a]	HR (95% CI)	Intake categories	Trend *P*
Hirayama (7)	1966–1982	Men	122 261	40+	Death	1454	↓	1.28 (0.56–2.92)	None vs. daily	0.003	NA			
		Women	142 857	40+	Death	463	—	0.87 (0.13–5.71)	None vs. daily	0.59	NA			
Ozasa et al. (10)	1988–1997	Men	42 940	40–79	Death	446	NA				NA			
		Women	55 308	40–79	Death	126	NA				NA			
Takezaki et al. (11)	1985–1999	Men and women	5885	30+	Incidence	51	—	1.06 (0.52–2.16)	5/week+ vs. <3/week	0.93	↓	0.61 (0.29–1.30)	5/week+ vs. <3/week	0.23
Sauvaget et al. (12)	1980–1998	Men and women	38 540	34–103	Death	563	—	0.95 (0.76–1.19)	Daily vs. 0–1/week	0.68	↓	0.80 (0.65–0.98)	Daily vs. 0–1/week	0.035
Liu et al. (13)	1990–1999	Men and women	93 338	40–69	Incidence	428	NA				—	1.16 (0.84–1.58)	T3 vs. T1	0.33[b]
Khan et al. (14)	1984–2002	Men	1524	40–97	Death	41	NA				—	0.8 (0.3–2.2)	Several times/week+ vs. less	NA
		Women	1634	40–97	Death	10	Insufficient number of cases							

CI, confidence interval; NA, not available; T1–T3, tertiles 1–3; HR, hazard ratio.
[a]↑↑↑ or ↓↓↓, strong; ↑↑ or ↓↓, moderate; ↑ or ↓, weak; —, no association (see Methods for more detailed definitions).
[b]Estimated from HRs with their 95% CIs by food intake category (see Methods for details of the procedure).

research group members, and was therefore somewhat subjective. To assure the validity of our systematic review, the authors of the articles along with other members of our research group evaluated the evidence tables (Tables 1 and 2) and the summary tables (Tables 3 and 4), and our conclusions were based on a consensus. Details of our evaluation methods have been published elsewhere (5).

MAIN FEATURES AND COMMENTS

Evidence from Individual Studies

We identified six cohort studies (Table 1) (7,10–14) and four case–control studies (Table 2) (15–18) on lung cancer risk and the consumption of vegetables and/or fruit. In addition, we identified an article by Iso and Kubota (19) on a cohort study, the findings of which were also reported by Ozasa et al. (10); the former article was not included in the present review, however, because it did not take smoking into account as a confounding factor. Three case–control studies used overlapping data from one cancer hospital. From these, we selected the study by Takezaki et al. (17) to include in our review, because one of the other two studies did not consider smoking habits (20) and the other used a less comprehensive dataset (21). Of the six cohort studies, three (7,11,13) were population based, in which subjects were enrolled from general populations in geographically defined areas. The endpoint was defined as the incidence of lung cancer in two of these studies (11,13) and as death from the cancer in the other four (7,10,12,14). All four case–control studies were hospital based (i.e. cases were recruited from arbitrarily selected hospitals); the control subjects were also selected from among patients in hospitals where cases were identified in all of these investigations (i.e. hospital controls).

All (10–14,17,18) but one cohort (7) and one case–control (15) study controlled for possible confounding effects of smoking, or limited their participants to those who had never smoked (16). Among the six cohort studies, three

Table 4. Summary of associations between lung cancer risk and consumption of vegetables and fruit in case-control studies of Japanese populations

Reference	Study period	Study subjects				Green-yellow vegetables				Fruit			
		Sex	Age (years)	Number of cases	Number of controls	Magnitude of association[a]	OR (95% CI or *P*)	Intake categories	Trend *P*	Magnitude of association[a]	OR (95% CI or *P*)	Intake categories	Trend *P*
Shimizu (15)	1975–1981	Men and women	NA	99	99	NA				↓?	0.8 (Kreyberg I, NS) 0.2 (Kreyberg II, NS)	Every day vs. ≤2/week	NA
Shimizu et al. (16)	1982–1985	Women	35–81	90	163	—	0.9 (NS)	3/week+ vs. <3/week	NA	—	1.2 (NS)	3/week+ vs. <3/week	NA
						—				—			
Takezaki et al. (17)	1988–1997	Men	40–79	748	2964	NA				—	0.76 (0.55–1.04)[b]	Every day vs. almost never	0.089[c]
		Women	40–79	297	1189	NA				↓	0.62 (0.28–1.36)[b]	Every day vs. almost never	0.064[c]
Matsuo et al. (18)	2001–2005	Men and women	NA	353	1757	↓	0.71 (0.53–0.97)[b]	T3 vs. T1	0.016[c]	—	0.84 (0.62–1.14)[b]	T3 vs. T1	0.20[c]

CI, confidence interval; NA, not available; NS, not significant; T1–T3, tertiles 1–3; OR, odds ratio.
[a]↑↑↑ or ↓↓↓, strong; ↑↑ or ↓↓, moderate; ↑ or ↓, weak; —, no association (see Methods for more detailed definitions).
[b]Based on a meta-analysis.
[c]Estimated from ORs with their 95% CIs by food intake category (see Methods for more details of the procedure).

presented results by gender (7,10,14), while the other three combined data for both genders (11–13). One case–control study (17) reported results by gender, two (15,18) combined data from men and women and the last (16) included only women. As mentioned in the 'Evaluation of results from individual studies' section, green-yellow vegetables and fruit were selected as food items to be analysed, because their inclusion was relatively common among the studies. Sufficient data were not available for other types of vegetable or for vegetables as a group.

The magnitudes of the associations for green-yellow vegetables and fruit are summarized in Tables 3 and 4 for cohort and case–control studies, respectively. Three cohort studies (7,11,12) and two case–control studies (16,18) reported findings on green-yellow vegetables. Only one cohort study (7) and one case–control study (18) showed a weak inverse association (↓) between lung cancer risk and consumption of these vegetables. In the case of fruit, two (11,12) out of four cohort studies (11–14) and one (17) out of four case–control studies (15–18) demonstrated a weak inverse association (↓). Although one additional study by Shimizu (15) showed a similar correlation, its magnitude was unclear because insufficient data were provided in the article to obtain summary ORs for all histological types (↓? in Table 4).

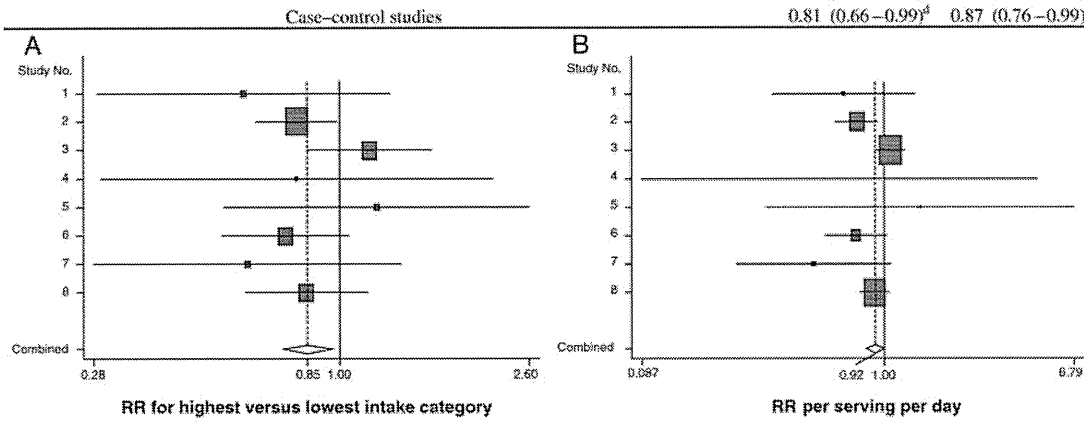
Summary Measures for Lung Cancer Risk and Fruit Consumption

The summary RR was estimated to be 0.85 (95% CI = 0.75–0.96) for the highest versus lowest intake category and 0.92 (95% CI = 0.84–1.00) per serving per day (Fig. 1, $P < 0.05$ for both). The cohort studies and the case–control studies provided reasonably consistent summary measures, although they did not reach statistical significance for the former. The inverse association between fruit consumption and lung cancer risk was consistently detected in the sensitivity analysis using 70–100 g for one serving, although it was somewhat attenuated when one serving was assumed to be 70 g. The summary RR (95% CI) was 0.93 (0.86–1.01), 0.92 (0.84–1.00), 0.90 (0.82–0.99) and 0.89 (0.80–0.98) for 70, 80, 90 and 100 g of serving size, respectively (a fixed-effect model for all the serving sizes; test for heterogeneity by the Q statistic: $P \geq 0.05$ for all).

Methodological Issues in the Reviewed Studies

Some methodological issues should be kept in mind when assessing the findings from these cohort and case–control studies.

Study No.	First author	Reference	Sex	Design	Event	Intake category: Highest	Intake category: Lowest	RR for highest versus lowest intake category	RR per serving per day (95% CI)
1	Takezaki	(11)	M+F	CH	Incidence	5+/week	<3/week	0.61 (0.29–1.30)	0.67 (0.33–1.36)[a]
2	Sauvaget	(12)	M+F	CH	Death	Daily	0-1/week	0.80 (0.65–0.98)	0.76 (0.61–0.94)[a]
3	Liu	(13)	M+F	CH	Incidence	Tertile 3	Tertile 1	1.16 (0.84–1.58)	1.07 (0.93–1.24)[a]
4	Khan	(14)	M	CH	Death	Several times+/week	≤Several times/month	0.8 (0.3–2.2)	0.64 (0.09–4.69)
5	Shimizu	(16)	F	CC		3+/week	<3/week	1.20 (0.55–2.61)[b]	1.44 (0.31–6.79)
6	Takezaki	(17)	M	CC		Every day	Almost never	0.76 (0.55–1.04)[c]	0.75 (0.55–1.03)[a]
7	Takezaki	(17)	F	CC		Every day	Almost never	0.62 (0.28–1.36)[c]	0.49 (0.23–1.07)[a]
8	Matsuo	(18)	M+F	CC		Tertile 3	Tertile 1	0.84 (0.62–1.14)[c]	0.91 (0.79–1.05)[a]
Summary estimates						Total		0.85 (0.75–0.96)[d]	0.92 (0.84–1.00)[d]
						Cohort studies		0.87 (0.74–1.03)[d]	0.88 (0.66–1.16)[e]
						Case–control studies		0.81 (0.66–0.99)[d]	0.87 (0.76–0.99)[d]



RR, relative risk; CI, confidence interval; CH, cohort study; CC, case-control study; M, male; F, female.
[a]Based on a weighted log-linear regression analysis.
[b]The CI was estimated from the distribution of fruit consumption among controls.
[c]Based on a meta-analysis.
[d]Based on a fixed-effect model (test for heterogeneity by the Q statistic: $P \geq 0.05$).
[e]Based on a random-effect model (test for heterogeneity by the Q statistic: $P < 0.05$).
Reference 15 was excluded because the standard errors of the odds ratios were unavailable.

Figure 1. Summary measures of the association between lung cancer risk and fruit consumption. (A) RR for the highest versus lowest intake category (fixed-effect model; test for heterogeneity: Q = 6.724, degrees of freedom [df] = 7, $P = 0.46$). (B) RR per serving per day (fixed-effect model; test for heterogeneity: Q = 12.689 with df = 7, $P = 0.080$).

First, vegetables and fruit might have been widely regarded as foods that reduce cancer risk, which could have resulted in a recall bias in case–control studies. Such a bias was suggested by the fact that greater risk reductions were found in case–control studies than in cohort studies as summarized in worldwide reviews (1,2).

Secondly, residual confounding effects due to smoking might have existed. Smokers tend to consume less fruit and vegetables (12,13), while also being at a higher risk of lung cancer (6). Although most of the studies reviewed here adjusted for smoking in their analyses, the method of adjustment varied among them. For example, one study categorized participants simply into never, former and current smokers (12), which might have resulted in residual confounding effects. Additionally, only one study (17) considered environmental tobacco smoke as a confounding factor.

Thirdly, methodological limitations in the assessment of vegetable and/or fruit intakes might have caused misclassifications. Of the studies listed in the evidence tables (Tables 1 and 2), only those published recently (10,12,13,18) validated the food frequency questionnaires used to estimate dietary intake. In general, the validity of intake assessment with a food frequency questionnaire tends to be lower for vegetables than for fruit (22). Moreover, two of the studies (10,17) related lung cancer risk to individual vegetables or fruit instead of their total consumption. Efforts to examine the risk of lung cancer associated with many food items might have produced a chance inverse correlation between cancer risk and some kinds of vegetables and/or fruit. We therefore evaluated the magnitude of the association only for food items that were common to several studies (i.e. green-yellow vegetables and fruit). One study (10) could not be included in this evaluation because the HRs or ORs were not available for either green-yellow vegetables or fruit.

If the consumption of vegetables and/or fruit decreases the risk of lung cancer, changes in diet and in the type of lung cancer might still attenuate the inverse associations. Because the intake of green-yellow vegetables has been increasing in Japan (23), many Japanese might now consume sufficient amounts to have a preventive effect on lung cancer, meaning that a clear elevation of risk might not emerge in analytical

epidemiological studies. In addition, the proportion of adenocarcinoma cases has been increasing among Japanese lung cancer cases (24). Some studies have reported a greater risk reduction associated with vegetable or fruit consumption for squamous cell carcinoma than for adenocarcinoma (1). The recent prevalence of adenocarcinoma might therefore have resulted in weaker associations between the consumption of vegetables and/or fruit and lung cancer risk.

Finally, potential publication bias cannot be ruled out. The failure of β-carotene supplementation to decrease lung cancer risk (4), and the lack of protective effects for vegetable consumption found in some large prospective studies (1) might have prompted some Japanese researchers to publish articles that reported no association between vegetable and/or fruit consumption and the risk of lung cancer.

Recently, Matsuo et al. (18) pointed out that the risk of lung cancer in cases without epidermal growth factor receptor (EGFR) mutation compared with those with the mutation tended to be more inversely correlated with the intake of green-yellow vegetables. Classifying lung cancer cases by molecular markers might be useful in identifying the subgroups for which risk can be reduced by increasing the consumption of vegetables.

Biological Plausibility

The suggested risk reduction achieved by consuming vegetables and fruit is biologically plausible (1,2), because these foods contain vitamin C and other antioxidant vitamins, carotenoids, phenols, flavonoids and other phytochemicals. These compounds might exert protective effects against lung cancer by modulating phase I and II enzymes and antioxidant enzymes, decreasing direct or indirect oxidative DNA damage and carcinogen–DNA binding, enhancing DNA repair, inhibiting the endogenous formation of carcinogens, modifying cell proliferation and apoptosis or stimulating the immune system (1,2). Vegetables are also sources of folate, which plays an important role in the synthesis and methylation of DNA (2). Thus, further prospective studies using well-validated methods of assessing the consumption of vegetables and/or fruit as food groups, rather than as individual food items, are needed to elucidate the relevance of these foods to the risk of lung cancer.

EVALUATION OF EVIDENCE ON LUNG CANCER RISK AND CONSUMPTION OF VEGETABLES AND FRUIT

Our review showed that fruit consumption possibly decreased the risk of lung cancer in Japan, whereas there was insufficient epidemiological evidence for an association between vegetable consumption and lung cancer risk. It is therefore likely that any protective effects of the consumption of fruit will be greater than those of the consumption of vegetables. This conclusion is based on the following evidence: first, our review revealed that fruit consumption showed an inverse association with the risk of lung cancer in more studies than vegetable intake (Tables 3 and 4). Secondly, the validity of the intake assessment tended to be lower for vegetables than for fruit (22). Thirdly, recent reviews by the World Cancer Research Fund and the American Institute for Cancer Research (3), which summarized international evidence, reported that the potential protective effects against lung cancer were more pronounced for fruit than for vegetables.

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Conflict of interest statement

None declared.

References

1. International Agency for Research on Cancer, World Health Organization. *IARC Handbooks of Cancer Prevention, vol. 8: Fruit and Vegetables*. Lyon: IARC Press 2003.
2. World Cancer Research Fund, American Institute for Cancer Research. Foods and drinks: vegetables, fruits, pulses (legumes), nuts, seeds, herbs, spices. In: *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*. Washington: American Institute for Cancer Research 2007;75–115.
3. World Cancer Research Fund, American Institute for Cancer Research. Cancers: lung. In: *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*. Washington: American Institute for Cancer Research 2007;259–64.
4. World Cancer Research Fund, American Institute for Cancer Research. Foods and drinks: dietary constituents and supplements. In: *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*. Washington: American Institute for Cancer Research 2007;179–89.
5. Inoue M, Tsuji I, Wakai K, Nagata C, Mizoue T, Tanaka K, et al. Evaluation based on systematic review of epidemiological evidence among Japanese populations: tobacco smoking and total cancer risk. *Jpn J Clin Oncol* 2005;35:404–11.
6. Wakai K, Inoue M, Mizoue T, Tanaka K, Tsuji I, Nagata C, et al. Tobacco smoking and lung cancer risk: an evaluation based on a systematic review of epidemiological evidence among the Japanese population. *Jpn J Clin Oncol* 2006;36:309–24.
7. Hirayama T. Diet and mortality. In: Wahrendorf J, ed. *Life-Style and Mortality: A Large-Scale Census-Based Cohort Study in Japan*. Basel: Karger 1990;73–95.
8. Pavia M, Pileggi C, Nobile CG, Angelillo IF. Association between fruit and vegetable consumption and oral cancer: a meta-analysis of observational studies. *Am J Clin Nutr* 2006;83:1126–34.
9. World Health Organization. *WHO Technical Reports Series 916. Diet, Nutrition, the Prevention of Chronic Disease. Report of a Joint WHO/FAO Expert Consultation*. Geneva: WHO 2003.

10. Ozasa K, Watanabe Y, Ito Y, Suzuki K, Tamakoshi A, Seki N, et al. Dietary habits and risk of lung cancer death in a large-scale cohort study (JACC Study) in Japan by sex and smoking habit. *Jpn J Cancer Res* 2001;92:1259–69.
11. Takezaki T, Inoue M, Kataoka H, Ikeda S, Yoshida M, Ohashi Y, et al. Diet and lung cancer risk from a 14-year population-based prospective study in Japan: with special reference to fish consumption. *Nutr Cancer* 2003;45:160–7.
12. Sauvaget C, Nagano J, Hayashi M, Spencer E, Shimizu Y, Allen N. Vegetables and fruit intake and cancer mortality in the Hiroshima/Nagasaki Life Span Study. *Br J Cancer* 2003;88:689–94.
13. Liu Y, Sobue T, Otani T, Tsugane S. Vegetables, fruit consumption and risk of lung cancer among middle-aged Japanese men and women: JPHC study. *Cancer Causes Control* 2004;15:349–57.
14. Khan MMH, Goto R, Kobayashi K, Suzumura S, Nagata Y, Sonoda T, et al. Dietary habits and cancer mortality among middle aged and older Japanese living in Hokkaido, Japan by cancer site and sex. *Asian Pac J Cancer Prev* 2004;5:58–65.
15. Shimizu H. A case-control study of lung cancer by histologic type. *Haigan* 1983;23:127–37 (in Japanese).
16. Shimizu H, Morishita M, Mizuno K, Masuda T, Ogura Y, Santo M, et al. A case-control study of lung cancer in nonsmoking women. *Tohoku J Exp Med* 1988;154:389–97.
17. Takezaki T, Hirose K, Inoue M, Hamajima N, Yatabe Y, Mitsudomi T, et al. Dietary factors and lung cancer risk in Japanese: with special reference to fish consumption and adenocarcinomas. *Br J Cancer* 2001;84:1199–206.
18. Matsuo K, Hiraki A, Ito H, Kosaka T, Suzuki T, Hirose K, et al. Soy consumption reduces the risk of non-small-cell lung cancers with epidermal growth factor receptor mutations among Japanese. *Cancer Sci* 2008;99:1202–8.
19. Iso H, Kubota Y. Nutrition and disease in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC). *Asian Pac J Cancer Prev* 2007;8 Suppl:35–80.
20. Huang XE, Hirose K, Wakai K, Matsuo K, Ito H, Xiang J, et al. Comparison of lifestyle risk factors by family history for gastric, breast, lung and colorectal cancer. *Asian Pac J Cancer Prev* 2004;5:419–27.
21. Gao CM, Tajima K, Kuroishi T, Hirose K, Inoue M. Protective effects of raw vegetables and fruit against lung cancer among smokers and ex-smokers: a case-control study in the Tokai area of Japan. *Jpn J Cancer Res* 1993;84:594–600.
22. Wakai K. A review of food frequency questionnaires developed and validated in Japan. *J Epidemiol* 2009;19:1–11.
23. The Research Group on Health and Nutrition Information. *The National Health and Nutrition Survey in Japan*, 2007. Tokyo: Dai-ichi Publishing 2010 (in Japanese).
24. Toyoda Y, Nakayama T, Ioka A, Tsukuma H. Trends in lung cancer incidence by histological type in Osaka, Japan. *Jpn J Clin Oncol* 2008;38:534–9.

Appendix

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