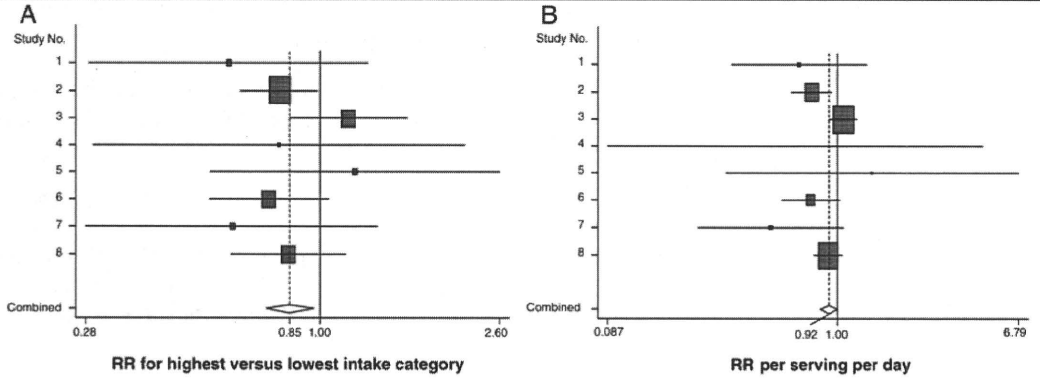
Study No.	First author	Reference	Sex	Design	Event	Intake category: Highest	Intake category: Lowest	RR for highest versus lowest intake category	RR per serving per day (95% CI)
1	Takezaki	(11)	M+F	CH	Incidence	5+/week	<3/week	0.61 (0.29 – 1.30)	0.67 (0.33 – 1.36)[a]
2	Sauvaget	(12)	M+F	CH	Death	Daily	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

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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.

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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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(1) **Alcohol Drinking and Esophageal Cancer Risk: An Evaluation Based on a Systematic Review of Epidemiologic Evidence among the Japanese Population**

Isao Oze, Keitaro Matsuo, Kenji Wakai, Chisato Nagata, Tetsuya Mizoue, Keitaro Tanaka, Ichiro Tsuji, Shizuka Sasazuki, Manami Inoue, Shoichiro Tsugane for the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan

Jpn J Clin Oncol 2011(in press)

Abstract

Although alcohol drinking is considered as an important risk factor for esophageal cancer, the magnitude of the association might be varied among geographic areas. Therefore, we reviewed epidemiologic studies on the association between alcohol drinking and esophageal cancer among Japanese population. Original data were obtained from MEDLINE searched using PubMed or from searches of the Ichushi database, complemented with manual searches. Evaluation of associations was based on the strength of evidence (`convincing', `probable', `possible', or `insufficient') and the magnitude of association (`strong', `moderate', `weak', or `no association'), together with biological plausibility as previously evaluated by the International Agency of Research on Cancer. We identified four cohort studies and nine case-control studies. All cohort studies and case-control studies showed strong positive associations between esophageal cancer and alcohol drinking. All cohort studies and six case-control studies showed that alcohol drinking had the dose- or frequency-response relationships with esophageal cancer. In addition, four case-control studies showed that ALDH2 Glu504Lys polymorphism had strong effect modification with alcohol drinking. We conclude that there is convincing evidence that alcohol drinking increases the risk of esophageal cancer in the Japanese population.

Key words: systematic review, epidemiology, alcohol drinking, esophageal cancer, Japanese

(2) **Association between body-mass-index (BMI) and the colorectal cancer risk in Japan: Pooled-analysis of population-based cohort studies in Japan.**

Keitaro Matsuo, Tetsuya Mizoue, Keitaro Tanaka, Ichro Tsuji, Yumi Sugawara, Shizuka Sasazuki, Chisato Nagata, Akiko Tamakoshi, Kenji Wakai, Manami Inoue, Shoichiro Tsugane for the Development and Evaluation of Cancer Prevention Strategies in Japan.

Ann Oncol 2011 (in press)

Abstract (200 words)

Background: Obesity has been recognized as important risk factors for colorectal cancer. However, limited evidence is available on colorectal cancer and BMI in Asian population.

Methods: We conducted a pooled analysis of eight population-based prospective cohorts studies in Japan with more than 300,000 subjects to evaluate an impact of obesity in terms of body-mass index (BMI) on colorectal cancer risk with unified categories. We estimated summary hazard ratio (HR) by pooling of study-specific HR for BMI categories with random effect model.

Results: We found a significant positive association between BMI and colorectal cancer risk in male and female. Adjusted hazard ratios (HRs) for 1 kg/m2 increase were 1.03 [95% confidence interval (CI): 1.02-1.40] for male and 1.02 (1.00-1.03) for female. The association was stronger in colon,

especially in proximal colon, relative to rectum. Males showed a stronger association than females. Population attrributable fraction for colorectal cancer by BMI 25 kg/m2 or more was 3.62% (1.91-5.30) for males and 2.62% (0.74-4.47) for females.

Conclusion: We found significant association between BMI and colorectal cancer risk by pooling of data from cohort studies with considerable number of subjects among Japanese population. This information is important in cancer control planning especially in Asian population.