Original Research Article

Dietary patterns and risk of esophageal cancer mortality: The Japan Collaborative Cohort Study

Emiko Okada[1], Koshi Nakamura[1], Shigekazu Ukawa[1], Kiyomi Sakata[2], Chigusa Date[3], Hiroyasu Iso[4], Akiko Tamakoshi[1,*]

[1]Department of Public Health, Hokkaido University Graduate School of Medicine, North 15 West 7 Kita-ku, Sapporo, 060-8638, Japan

[2]Department of Hygiene and Preventive Medicine, Iwate Medical University, 2-1-1 Nishitokuta, Yahaba, 028-3694, Japan

[3]Department of Food Science and Nutrition, School of Human Science and Environment, University of Hyogo, 1-1-12 Shinzaike-Honcho, Himeji, Hyogo, 670-0092, Japan

[4]Public Health, Department of Social and Environmental Medicine, Graduate School of Medicine, Osaka University, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan

Running title: Dietary patterns and esophageal cancer

***Corresponding author:** Akiko Tamakoshi, Department of Public Health Sciences,

Hokkaido University Graduate School of Medicine, North 15 West 7 Kita-ku, Sapporo, 060-8638, Japan.

Tel: +81-11-706-5068; Fax: +81-11-706-7805;

E-mail: tamaa@med.hokudai.ac.jp

Abbreviations:

BMI, body mass index

CI, confidence interval

EA, esophageal adenocarcinoma

EC, esophageal cancer

ESCC, esophageal squamous cell carcinoma

FFQ, food frequency questionnaire

HR, hazard ratio

ICD, International Classification of Disease

JACC study, Japan Collaborative Cohort Study

ABSTRACT

Several case-control studies have associated dietary patterns with esophageal cancer (EC) risk, but prospective studies are scarce. We investigated dietary pattern and EC mortality risk associations by smoking status. Participants were 26,562 40 to 79-year-old Japanese men, who enrolled in the Japan Collaborative Cohort Study between 1988 and 1990. Hazard ratios (HR) and 95% confidence intervals (CIs) for EC mortality in nonsmokers and smokers were estimated using Cox proportional models. During follow-up (1988–2009), 132 participants died of EC. Using a baseline food frequency questionnaire and factor analysis, vegetable, animal, and dairy product food patterns were identified. EC risk decreased significantly with a higher factor score for the dairy product pattern (P_{trend} = 0.042) and was more pronounced in smokers (multivariable HR [4th vs. 1st quartiles]) = 0.57, 95% CI: 0.30, 1.09; P_{trend} = 0.021). Neither vegetable nor animal food patterns were significant overall; however, EC risk increased with a higher factor score for the animal food pattern in nonsmokers (multivariable HR [4th vs. 1st quartiles]) = 6.01, 95% CI: 1.17, 30.88; P_{trend} = 0.021), although the small number of events was a limitation. Our findings suggest a dairy product pattern may reduce EC risk in Japanese men, especially smokers.

Key words: dietary pattern, Japanese, esophageal cancer, cohort study, epidemiological study

Introduction

Esophageal cancer is the eighth most common type of cancer and the sixth most common cause of death from cancer worldwide [1]. There are two main histological types of esophageal cancer: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EA). The development of each specific type is different depending on race and geographical region. EA is increasing in Western countries, whereas ESCC is the dominant type of esophageal cancer in East Asian countries such as China, Korea, and Japan [2]. Risk factors for esophageal cancer are tobacco smoking, heavy alcohol drinking, and frequent consumption of high-temperature beverages [3]. In contrast, the epidemiological literature has suggested that high consumption of fruit and vegetables is associated with a lower risk of esophageal cancer [4]. However, more thorough evaluations of dietary patterns are needed to assess the effect of dietary intakes on esophageal cancer risk, because a diet encompasses more than single nutrients and foods.

Several studies have reported the associations between dietary patterns, or a diet index, and esophageal cancer in epidemiological case-control studies [5-9]. In a recent meta-analysis that included nine case-control studies, three common dietary patterns based on high intakes of foods/nutrients were indicated via principle component factor analysis: Western, healthy, and drink/alcohol patterns [10]. This meta-analysis suggested that the healthy pattern was associated with a decreased risk of ESCC, whereas drink/alcohol patterns were associated with an increased risk, but no significant association was observed

between a Western pattern and ESCC. A review of 24 case-control studies that investigated the relationship between dietary patterns and upper aerodigestive tract cancers (including the oral cavity, esophagus, pharynx, and larynx) also have suggested that dietary patterns based on high intakes of fruit and/or vegetables or nutrients have a beneficial role, whereas patterns of heavy alcohol consumption are detrimental [11]. In a prospective cohort study in the United States, individuals scoring higher on the Healthy Eating Index-2005 and an alternate Mediterranean-style diet have been inversely associated with risk for ESCC [12]. In the past, predominantly case-control studies have been used to investigate the association between dietary patterns and esophageal cancer mortality. Moreover, dietary patterns or indexes used in previous studies were designed for populations in Western and West Asian countries. No reports have examined the relationship between dietary patterns and esophageal cancer in East Asian populations, including the Japanese who have dietary patterns that differ from those in the other populations.

The objectives of this study were to determine whether dietary patterns are associated with the risk of esophageal cancer mortality among Japanese populations in the Japan Collaborative Cohort (JACC) Study. In addition, we investigated whether the aforementioned associations were modified by smoking, which is not only a major risk factor for esophageal cancer [13] but is still a popular lifestyle choice among many East Asian males [14].

Material and Methods

Study population

Between 1988 and 1990, subjects were enrolled to participate in the JACC Study and evaluated for cancer risk via assessment of the impact that lifestyle factors had on their health. Details of the study design have been described elsewhere [15]. Briefly, 110,585 (46,395 men and 64,190 women) participants aged 40–79 years from 45 regions throughout Japan were enrolled. Participants were mostly recruited during a health checkup; they completed a self-administered questionnaire. Of the 110,585 participants, 64,190 women were excluded from the analysis because the number of cases of esophageal cancer among them was very low and it was uncertain if sufficient statistical power could be obtained for the multivariate analysis. In addition, men with a history of cancer at baseline (n = 411), men who were missing information for more than five food items in the self-administered food frequency questionnaire (FFQ) (n = 18,294) or missing information on smoking status (n = 1,128) were also excluded. A total of 26,562 participants were included in the analysis for this study. The study design was approved by the Ethical Board of Nagoya University School of Medicine.

Dietary assessment

Information on the intake of 39 food items was assessed from a previously validated self-administered questionnaire including a FFQ at baseline [16]. Most food items were

assessed for five frequency categories: rarely, 1–2 times/month, 1–2 times/week, 3–4 times/week, and almost daily. Rice and miso-soup intake were assessed using the number of bowls consumed daily. Beverages were assessed for five frequency categories: almost never, 1–2 cups/month, 1–2 cups/week, 3–4 cups/week, and almost daily for green tea, tea, oolong tea, and coffee. For participants who had blanks for information of four or less items in the FFQ, the missing data were replaced with the median values applicable to their geographical region [17, 18]. Alcohol consumption was assessed for frequency using the following categories: never, former, and current drinker (<1 time/week, 1–2 times/week, 3–4 times/week, and almost daily). Total energy and nutrient intakes were estimated based on the fifth edition of the Japan Food Table, and intake of nutrients and specific foods from food groups were adjusted for total energy intake by residual methods [19].

Follow-up

Mortality data were centralized at the Ministry of Health and Welfare and the underlying causes of deaths were coded using National Vital Statistics codes which were in accordance with the 10th revision of the International Classification of Disease (ICD-10). Follow-up was completed at the end of 2009 in most regions; however, it was stopped at the end of 1999 in 4 regions, at the end of 2003 in another 4 regions, and at the end of 2008 in 2 regions. Participants who moved away from their region during the study were treated as censored cases. Death from esophageal cancer was determined by the coding C15.

Statistical analysis

Dietary patterns based on the various food items were analyzed by factor analysis using a varimax rotation. To determine the number of factors to be retained, we considered components with an eigenvalue greater than 1.0, scree test results, and interpretability of the factors. Factor scores were calculated for each of the participants, standardized to a mean value of zero and a standard deviation of one, and each participant was assigned a factor score for every identified pattern.

Participants were divided into four categories based on quartiles of factor scores for dietary patterns. Age-adjusted and multivariate hazard ratios (HRs) and 95% confidence intervals (CI) for mortality risk related to esophageal cancer were evaluated based on dietary patterns in the second through fourth quartiles and compared to those in the first quartiles using the Cox proportional hazard model. Another model, used to assess the linear relationship, was created and P_{trend} values were obtained using the quartile factor scores for the dietary patterns as ordinal variables. The following variables were included in the multivariate models: age (continuous variable), geographical region, body mass index (BMI) (<18.5, 18.5–24.9, or ≥25.0 kg/m^2, or unknown), education duration (<13 years, ≥13 years, or unknown), smoking status (never, former, or current smoker), frequency of alcohol consumption (never, former, current drinker [<1 time/week, 1–2 times/week, 3–4 times/week, or almost daily], or unknown) and total daily energy intake (<1,396, 1,396–

1,718, 1,719–2,076, or ≥2,077 kcal/day, or unknown). Further, we performed a stratified analysis by smoking status using the following definitions: smoker, current smoker or former smoker who quit <10 years ago; nonsmoker, never smoker or former smoker who quit ≥10 years ago. All statistical analyses were performed using the SAS statistical package for Windows (version 9.4, SAS). Differences were considered statistically significant at $p < 0.05$.

Results

At baseline, three dietary patterns were extracted using factor analysis in this study. The factor-loading matrix for dietary patterns and food items are shown in Table 1. The first pattern had a higher loading of vegetable (carrots, cabbage, spinach, Chinese cabbage, and tomatoes), algae, potatoes, tofu, fungi, citrus fruit, other fruit, fresh fish, and boiled beans. The second pattern had a higher loading of meat (chicken, ham, liver, pork, and beef), deep-fried foods, fried vegetables, and dried fish. The third pattern had a higher loading of dairy products (cheese, yogurt and butter), milk, margarine, coffee, and tea. These three patterns were labelled as follows: vegetable pattern, animal food pattern, and a dairy product pattern. The total cumulative variance of these three dietary patterns was 25.1%.

Demographic baseline characteristics of participants are shown according to the three dietary patterns by score quartile in Table 2. Participants in a high quartile for the vegetable pattern were older and more educated, and less likely to be a current smoker and

current drinker. Compared with participants in the low quartile for the animal food pattern, participants in higher quartiles were younger in age, had lower educational levels, and were more likely to be a heavier drinker. For the dairy product pattern, participants in the higher quartile of intake were younger in age, had more education, and were less likely to be a smoker and a drinker compared with participants in the low quartile for this pattern.

The median follow-up period was 18.9 years. During 424,646 person-years, there were 132 deaths attributed to esophageal cancer. Table 3 shows the results of the Cox proportional hazard model between the three dietary patterns and esophageal cancer mortality. There were no remarkable differences in multivariate HRs for esophageal cancer mortality among the quartiles of vegetable and animal food patterns. However, the multivariate HRs tended to decrease when factor score of the dairy product pattern was higher, as evidenced by a significant linear relationship (P = 0.042).

The HRs for esophageal cancer mortality associated with the three dietary patterns according to smoking status are shown in Table 4. Among smokers, multivariate HRs for the dairy product pattern decreased for the three highest quartiles compared with the lowest quartile and ranged from 0.76 (95% CI: 0.47, 1.23) to 0.57 (95% CI: 0.30, 1.09), with a dose-response relationship (P = 0.021); however, this association was not observed among nonsmokers. Multivariate HRs for the animal food pattern in the highest quartiles compared with the lowest quartile were 6.01 (95% CI: 1.17, 30.88) among nonsmokers (P = 0.021). Statistically significant associations between a vegetable pattern and esophageal cancer

mortality were not observed among both smokers and nonsmokers.

Discussion

We identified three major dietary patterns that we referred to as vegetable, animal food, and dairy product patterns when we evaluated data from Japanese men that participated in a large prospective cohort study. The dairy product pattern showed an inverse association with the risk of esophageal cancer, especially among smokers, whereas the animal food pattern showed an increased risk of esophageal cancer among nonsmokers. The vegetable pattern was not associated with esophageal cancer mortality.

The vegetable pattern was a dietary pattern equivalent to a “traditional” Japanese diet which is characterized by frequent intakes of vegetables, algae, potatoes, soy products, fungi, fruit, and fresh fish. This dietary pattern was similar to that of others classified as a “healthy diet” or a “prudent diet” in previous studies performed in other countries [5, 7, 8]. In a meta-analysis based only on case-control studies, the healthy pattern was associated with a decreased risk of ESCC (odds ratio [OR]: 0.36; 95% CI: 0.23, 0.49) [10]. HRs for the highest quintile scores based on the alternate Mediterranean-style diet (score 0–2) for esophageal cancer were 0.44 (95%CI: 0.22, 0.88) compared with the lowest quintile (score 7–9) in a large cohort study in the United States [12]. Several other prospective cohort studies have reported that the intake of fruit and vegetables shows an inverse association with esophageal cancer [20-22]. In contrast, no significant association between the vegetable pattern and

esophageal cancer was observed in the present study. When the effects of a dietary pattern characterized by a high intake of vegetables, rather than specific foods, were prospectively assessed among Japanese people, it appeared to be less effective at reducing the risk for esophageal cancer.

The animal food pattern was similar to dietary patterns known as “Western diets,” which are characterized by a high intake of meat, and fried and high-fat foods as described in previous studies [5, 7, 8]. One meta-analysis has reported no association between a Western pattern and esophageal cancer (OR: 1.29; 95%CI: 0.83, 1.75) [10]. More recently published studies have shown that red meat and processed meat are a risk factor for esophageal cancer [23, 24]. On the basis of a stratified analysis by smoking status, we also determined that an animal food pattern was associated with an increased risk for esophageal cancer in nonsmokers, although a significant association was not observed in the study population as a whole. Meat and processed meat with a higher loading in the animal food pattern, have been shown to exhibit potential mechanisms for carcinogenic effects via the formation of heterocyclic amines and polycyclic aromatic hydrocarbons at high cooking temperatures, due to the pro-oxidant activity of heme iron and as a consequence of the N-nitroso compounds they contain [25, 26]. Taken together, the animal food pattern may be a risk factor for esophageal cancer among Japanese men, independent of smoking status, which is a known risk factor for esophageal cancer [13]. However, caution should be used when interpreting our results because the number of deaths attributable to esophageal cancer in our study was very low in

nonsmokers, especially for those with the lowest intake of animal food pattern.

We found that the dairy product pattern was associated with a decreased risk of esophageal cancer mortality, but only among smokers. To our knowledge, this is the first report establishing a relationship between a dairy product pattern and the risk of esophageal cancer mortality in a prospective study. Consumption of dairy products, including milk, cheese, and yogurt, was inversely associated with esophageal cancer in a case-control study performed in central and eastern Europe [27], but the association with dietary patterns was not investigated. The decreased risk of developing upper aerodigestive tract cancer that was associated with a high intake of yoghurt has been reported in a Japanese case-control study [28]. The dairy product pattern was dominated by a higher factor-loading of coffee and tea in our data. Previous cohort studies have reported that coffee and tea consumption were associated with a lower risk of esophageal cancers among current smokers [29, 30]. Furthermore, while the factor-loading of fruit was lower in the dairy product pattern compared with the vegetable pattern, it was still relatively high. Oxidative DNA damage attributable to smoking is related to esophageal carcinogenesis and its progression [31, 32]. Dairy products, milk, coffee, tea, and fruit are potential sources of substances with anticarcinogenic effects such as vitamin D, conjugated linoleic acid, vitamin C, folate, and polyphenols including flavonoids [33-38]. The dietary pattern which combined the foods with anticarcinogenic activities may have augmented the protective effect against esophageal cancer in smokers. Our findings suggest that a dietary pattern high in dairy, coffee, tea, and fruit, which is representative of the dairy

product pattern, had a protective effect against potential mechanisms, such as oxidative DNA damage, by which smoking can cause pathologic alterations that can increase the risk of esophageal cancer.

A strength of the present cohort study relates to its prospective observation of a large number of study participants who were recruited nationwide in Japan. Another strength is that we examined associations of interest and we also adjusted for potential confounders. However, the present study has some limitations. First, our dietary questionnaire evaluated rice intake, because it is the most common staple of Japan, but it did not focus on grain consumption related to bread, noodle, or cereal intake. Second, dietary habits of participants were assessed only at baseline and might have changed during the follow-up period; however, this type of data collection methodology is commonly used for epidemiological studies. Third, a large number of participants who had missing data pertaining to their dietary habits were excluded from the analyses. However, most baseline characteristics (such as BMI, marriage status, smoking status, and alcohol drinking) were similar between participants and those excluded from the study; two exceptions were age (56.2 years for study participants vs. 59.4 years for those excluded from the study) and education duration ≥13 years (18.8 % vs. 13.6 %, respectively). We therefore consider that bias was unlikely in the present study, despite the slight differences in baseline characteristics. Fourth, we evaluated the risk of esophageal cancer without consideration of histological type because we had no data on the type.

In conclusion, a dairy product pattern was associated with a decrease in the risk of esophageal cancer mortality among Japanese men who were smokers. Our findings suggest that the dairy product pattern was beneficial for smokers who were at high-risk for esophageal cancer.

Acknowledgements

We wish to express our sincere thanks to Drs. Kunio Aoki and Yoshiyuki Ohno, Professors Emeritus of the Nagoya University School of Medicine and former chairpersons of the JACC Study. For their encouragement and support during this study, we are also greatly indebted to: Dr. Haruo Sugano, former Director of the Cancer Institute, Tokyo, who made substantial contributions to the initiation of the JACC Study; Dr. Tomoyuki Kitagawa, Director Emeritus of the Cancer Institute of the Japanese Foundation for Cancer Research and former project leader of the Grant-in-Aid for Scientific Research on Priority Area ‘Cancer’; Dr. Kazuo Tajima, Aichi Cancer Center, who was the previous project leader of the Grant-in-Aid for Scientific Research on Priority Area of Cancer Epidemiology. This work was supported by: Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (MEXT) (Monbusho); Grants-in-Aid for Scientific Research on Priority Areas of Cancer; and Grants-in-Aid for Scientific Research on Priority Areas of Cancer Epidemiology from MEXT (MonbuKagaku-sho) (Nos. 61010076, 62010074, 63010074, 1010068, 2151065, 3151064,

4151063, 5151069, 6279102, 11181101, 17015022, 18014011, 20014026, and 20390156).

Funding

This study was funded by: Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (MEXT); Grants-in-Aid for Scientific Research on Priority Areas of Cancer; and Grants-in-Aid for Scientific Research on Priority Areas of Cancer Epidemiology from MEXT.

Ethics approval

This study was approved by the Ethical Board of Nagoya University School of Medicine.

Conflict of interest

All authors declare that there are no conflicts of interests.

Appendix: Members of the Japan Collaborative Cohort Study Group

The present members of the JACC Study Group who coauthored this paper include: Dr. Akiko Tamakoshi (present chairperson of the study group), Hokkaido University Graduate School of Medicine; Drs. Mitsuru Mori and Fumio Sakauchi, Sapporo Medical University School of Medicine; Dr. Yutaka Motohashi, Akita University School of Medicine; Dr. Ichiro Tsuji, Tohoku University Graduate School of Medicine; Dr. Yosikazu Nakamura,

Jichi Medical School; Dr. Hiroyasu Iso, Osaka University School of Medicine; Dr. Haruo Mikami, Chiba Cancer Center; Dr. Michiko Kurosawa, Juntendo University School of Medicine; Dr. Yoshiharu Hoshiyama, Yokohama Soei University; Dr. Naohito Tanabe, University of Niigata Prefecture; Dr. Koji Tamakoshi, Nagoya University Graduate School of Health Science; Dr. Kenji Wakai, Nagoya University Graduate School of Medicine; Dr. Shinkan Tokudome, National Institute of Health and Nutrition; Dr. Koji Suzuki, Fujita Health University School of Health Sciences; Dr. Shuji Hashimoto, Fujita Health University School of Medicine; Dr. Shogo Kikuchi, Aichi Medical University School of Medicine; Dr. Yasuhiko Wada, Faculty of Nutrition, University of Kochi; Dr. Takashi Kawamura, Kyoto University Center for Student Health; Dr. Yoshiyuki Watanabe, Kyoto Prefectural University of Medicine Graduate School of Medical Science; Dr. Kotaro Ozasa, Radiation Effects Research Foundation; Dr. Tsuneharu Miki, Kyoto Prefectural University of Medicine Graduate School of Medical Science; Dr. Chigusa Date, School of Human Science and Environment, University of Hyogo; Dr. Kiyomi Sakata, Iwate Medical University; Dr. Yoichi Kurozawa, Tottori University Faculty of Medicine; Drs. Takesumi Yoshimura and Yoshihisa Fujino, University of Occupational and Environmental Health; Dr. Akira Shibata, Kurume University; Dr. Naoyuki Okamoto, Kanagawa Cancer Center; and Dr. Hideo Shio, Moriyama Municipal Hospital.

References

1. Ferlay J SI, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN, Estimated Cancer Incidence and Mortality Worldwide in 2012. *International Agency for Reseach on Cancr* 2012.

2. Zhang HZ, Jin GF, Shen HB. Epidemiologic differences in esophageal cancer between Asian and Western populations. *Chinese journal of cancer* 2012; **31**(6): 281-6.

3. Kamangar F, Chow WH, Abnet CC, Dawsey SM. Environmental causes of esophageal cancer. *Gastroenterology clinics of North America* 2009; **38**(1): 27-57, vii.

4. Liu J, Wang J, Leng Y, Lv C. Intake of fruit and vegetables and risk of esophageal squamous cell carcinoma: a meta-analysis of observational studies. *International journal of cancer Journal international du cancer* 2013; **133**(2): 473-85.

5. Bahmanyar S, Ye W. Dietary patterns and risk of squamous-cell carcinoma and adenocarcinoma of the esophagus and adenocarcinoma of the gastric cardia: a population-based case-control study in Sweden. *Nutrition and cancer* 2006; **54**(2): 171-8.

6. Bravi F, Edefonti V, Randi G, et al. Dietary patterns and the risk of esophageal cancer. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* 2012; **23**(3): 765-70.

7. De Stefani E, Deneo-Pellegrini H, Boffetta P, et al. Dietary patterns and risk of cancer: a factor analysis in Uruguay. *International journal of cancer Journal international du cancer* 2009; **124**(6): 1391-7.

8. Hajizadeh B, Rashidkhani B, Rad AH, Moasheri SM, Saboori H. Dietary patterns and risk of oesophageal squamous cell carcinoma: a case-control study. *Public health nutrition* 2010; **13**(7): 1107-12.

9. Navarro Silvera SA, Mayne ST, Risch HA, et al. Principal component analysis of dietary and lifestyle patterns in relation to risk of subtypes of esophageal and gastric cancer. *Annals of epidemiology* 2011; **21**(7): 543-50.

10. Liu X, Wang X, Lin S, Yuan J, Yu IT. Dietary patterns and oesophageal squamous cell carcinoma: a systematic review and meta-analysis. *British journal of cancer* 2014; **110**(11): 2785-95.

11. Bravi F, Edefonti V, Randi G, Ferraroni M, La Vecchia C, Decarli A. Dietary patterns and upper aerodigestive tract cancers: an overview and review. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* 2012; **23**(12): 3024-39.

12. Li WQ, Park Y, Wu JW, et al. Index-based dietary patterns and risk of esophageal and gastric cancer in a large cohort study. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2013; **11**(9): 1130-6.e2.

13. Oze I, Matsuo K, Ito H, et al. Cigarette smoking and esophageal cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. *Japanese journal of clinical oncology* 2012; **42**(1): 63-73.

14. Development OfECa. OECD Health Statistics. 2014.

15. Tamakoshi A, Ozasa K, Fujino Y, et al. Cohort profile of the Japan Collaborative Cohort Study at final follow-up. *Journal of epidemiology / Japan Epidemiological Association* 2013; **23**(3): 227-32.

16. Date C, Fukui M, Yamamoto A, et al. Reproducibility and validity of a self-administered food frequency questionnaire used in the JACC study. *Journal of epidemiology / Japan Epidemiological Association* 2005; **15 Suppl 1**: S9-23.

17. Pham TM, Fujino Y, Kikuchi S, Tamakoshi A, Matsuda S, Yoshimura T. Dietary patterns and risk of stomach cancer mortality: the Japan collaborative cohort study. *Annals of epidemiology* 2010; **20**(5): 356-63.

18. Maruyama K, Iso H, Date C, et al. Dietary patterns and risk of cardiovascular deaths among middle-aged Japanese: JACC Study. *Nutrition, metabolism, and cardiovascular diseases : NMCD* 2013; **23**(6): 519-27.

19. Willett W, Howe G, Kushi L. Adjustment for total energy intake in epidemiologic studies. *Am J Clin Nutr* 1997; **65**: 1220S-8S.

20. Freedman ND, Park Y, Subar AF, et al. Fruit and vegetable intake and esophageal cancer in a large prospective cohort study. *International journal of cancer Journal international du cancer* 2007; **121**(12): 2753-60.

21. Steevens J, Schouten LJ, Goldbohm RA, van den Brandt PA. Vegetables and fruits consumption and risk of esophageal and gastric cancer subtypes in the Netherlands Cohort

Study. *International journal of cancer Journal international du cancer* 2011; **129**(11): 2681-93.

22. Yamaji T, Inoue M, Sasazuki S, et al. Fruit and vegetable consumption and squamous cell carcinoma of the esophagus in Japan: the JPHC study. *International journal of cancer Journal international du cancer* 2008; **123**(8): 1935-40.

23. Choi Y, Song S, Song Y, Lee JE. Consumption of red and processed meat and esophageal cancer risk: meta-analysis. *World journal of gastroenterology : WJG* 2013; **19**(7): 1020-9.

24. Salehi M, Moradi-Lakeh M, Salehi MH, Nojomi M, Kolahdooz F. Meat, fish, and esophageal cancer risk: a systematic review and dose-response meta-analysis. *Nutrition reviews* 2013; **71**(5): 257-67.

25. Cross AJ, Pollock JR, Bingham SA. Haem, not protein or inorganic iron, is responsible for endogenous intestinal N-nitrosation arising from red meat. *Cancer research* 2003; **63**(10): 2358-60.

26. Cross AJ, Sinha R. Meat-related mutagens/carcinogens in the etiology of colorectal cancer. *Environmental and molecular mutagenesis* 2004; **44**(1): 44-55.

27. Sapkota A, Hsu CC, Zaridze D, et al. Dietary risk factors for squamous cell carcinoma of the upper aerodigestive tract in central and eastern Europe. *Cancer causes & control : CCC* 2008; **19**(10): 1161-70.

28. Kawakita D, Sato F, Hosono S, et al. Inverse association between yoghurt intake

and upper aerodigestive tract cancer risk in a Japanese population. *European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP)* 2012; **21**(5): 453-9.

29. Naganuma T, Kuriyama S, Kakizaki M, et al. Coffee consumption and the risk of oral, pharyngeal, and esophageal cancers in Japan: the Miyagi Cohort Study. *American journal of epidemiology* 2008; **168**(12): 1425-32.

30. Zamora-Ros R, Lujan-Barroso L, Bueno-de-Mesquita HB, et al. Tea and coffee consumption and risk of esophageal cancer: the European prospective investigation into cancer and nutrition study. *International journal of cancer Journal international du cancer* 2014; **135**(6): 1470-9.

31. Lin CS, Wang LS, Chou TY, et al. Cigarette smoking and hOGG1 Ser326Cys polymorphism are associated with 8-OHdG accumulation on mitochondrial DNA in thoracic esophageal squamous cell carcinoma. *Annals of surgical oncology* 2013; **20 Suppl 3**: S379-88.

32. Kubo N, Morita M, Nakashima Y, et al. Oxidative DNA damage in human esophageal cancer: clinicopathological analysis of 8-hydroxydeoxyguanosine and its repair enzyme. *Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus / ISDE* 2014; **27**(3): 285-93.

33. Giovannucci E, Liu Y, Rimm EB, et al. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. *Journal of the National Cancer*

Institute 2006; **98**(7): 451-9.

34. McCrorie TA, Keaveney EM, Wallace JM, Binns N, Livingstone MB. Human health effects of conjugated linoleic acid from milk and supplements. *Nutrition research reviews* 2011; **24**(2): 206-27.

35. Fang M, Chen D, Yang CS. Dietary polyphenols may affect DNA methylation. *The Journal of nutrition* 2007; **137**(1 Suppl): 223s-8s.

36. Rossi M, Garavello W, Talamini R, et al. Flavonoids and risk of squamous cell esophageal cancer. *International journal of cancer Journal international du cancer* 2007; **120**(7): 1560-4.

37. Terry P, Lagergren J, Ye W, Nyren O, Wolk A. Antioxidants and cancers of the esophagus and gastric cardia. *International journal of cancer Journal international du cancer* 2000; **87**(5): 750-4.

38. Xiao Q, Freedman ND, Ren J, Hollenbeck AR, Abnet CC, Park Y. Intakes of folate, methionine, vitamin B6, and vitamin B12 with risk of esophageal and gastric cancer in a large cohort study. *British journal of cancer* 2014; **110**(5): 1328-33.

Table 1. Factor loading matrix for three dietary patterns

	Vegetable pattern	Animal food pattern	Dairy product pattern
Rice	0.05	0.19	-0.39
Miso soup	0.35	0.04	-0.26
Beef	-0.12	0.34	0.23
Pork (excluding ham, sausage)	0.16	0.47	0.07
Ham or sausage	0.07	0.53	0.18
Chicken	0.14	0.54	0.02
Liver	0.01	0.47	0.05
Egg	0.32	0.23	0.08
Fresh fish	0.42	0.21	-0.11
Kamaboko (fish paste)	0.10	0.49	0.01
Dried fish or salted fish	0.26	0.41	-0.16
Milk	0.23	-0.02	0.35
Yogurt	0.08	0.10	0.40
Cheese	0.08	0.24	0.47
Butter	-0.02	0.27	0.51
Margarine	-0.02	0.16	0.57
Deep-fried foods or tempura	0.19	0.54	-0.01
Fried vegetables	0.36	0.42	-0.07
Spinach or garland chrysanthemum	0.59	0.14	0.01
Carrots or pumpkin	0.64	0.12	0.07
Tomatoes	0.42	0.17	0.01
Cabbage or head lettuce	0.60	0.15	0.11
Chinese cabbage	0.59	0.12	0.02
Edible wild plants	0.25	0.32	-0.10
Fungi	0.50	0.17	0.09
Potatoes	0.64	0.05	0.13
Algae (seaweed)	0.63	0.08	0.05
Pickles	0.34	0.08	-0.08
Preserved foods using soy sauce	0.21	0.32	0.04
Boiled beans	0.35	0.19	0.15
Tofu	0.54	0.10	-0.05
Citrus fruit	0.49	-0.07	0.33
Fresh fruits juice	0.22	0.16	0.22
Fruit (excluding citrus variety)	0.54	-0.06	0.38
Sweets	0.23	0.16	0.15
Coffee	0.02	-0.13	0.44
Tea	0.00	0.07	0.34
Green tea	0.12	0.01	0.03
Oolong tea	0.05	-0.05	0.27
Eigenvalue	5.9	2.1	1.9
Factor variance explained, %	15.0	5.3	4.8
Factor variance cumulative, %	15.0	20.3	25.1

Table 2. Baseline characteristics of three dietary patterns by factor score quartiles

Characteristics	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Vegetable pattern				
Mean age, years (SD)	54.2 (10.0)	55.7 (10.0)	56.7 (9.9)	58.2 (9.8)
Mean of BMI, kg/m^2 (SD)	22.7 (2.8)	22.7 (3.5)	22.7 (2.7)	22.8 (2.7)
Education ≥13 years, %	17.1	16.5	17.4	17.9
Married, %	86.7	90.1	90.5	90.6
Current smoker, %	60.8	54.7	51.2	47.9
Frequency of alcohol drinking				
Current drinker				
<1 time/week, %	5.0	3.8	4.1	4.2
1–2 time/week, %	6.5	6.9	7.0	6.2
3–4 time/week, %	10.0	10.1	9.7	10.5
almost daily, %	53.8	54.4	52.4	49.7
Former drinker, %	5.1	5.1	6.0	7.0
Nondrinker, %	17.3	17.0	17.7	19.6
Mean total energy intake, kcal/day (SD)	1,548 (477)	1,715 (470)	1,811 (485)	1,941 (499)
Animal food pattern				
Mean age (years) (SD)	56.9 (10.4)	56.2 (10.1)	55.8 (9.8)	55.9 (9.7)
Mean of BMI (kg/m^2) (SD)	22.8 (3.1)	22.7 (2.7)	22.7 (2.8)	22.6 (3.2)
Education ≥13 years, %	20.1	17.9	16.2	14.8
Married, (%)	88.6	90.2	90.0	89.0
Current smoker, %	50.9	54.9	53.9	55.0
Frequency of alcohol drinking				
Current drinker				
<1 time/week, %	5.6	4.2	4.0	3.4
1–2 time/week, %	8.0	7.0	6.1	5.4
3–4 time/week, %	10.1	10.5	9.5	10.0
almost daily, %	40.1	51.5	57.7	61.0
Former drinker, %	8.1	5.9	5.0	4.2
Nondrinker, %	24.5	18.5	15.5	13.1
Mean total energy intake, kcal/day (SD)	1,491 (426)	1,653 (437)	1,808 (449)	2,062 (514)
Dairy product pattern				
Mean age, years (SD)	57.0 (9.2)	56.1 (10.0)	55.6 (10.2)	56.1 (10.5)
Mean BMI, kg/m^2 (SD)	22.7 (3.4)	22.7 (2.8)	22.8 (2.8)	22.7 (2.8)
Education ≥13 years, %	9.1	14.4	18.7	26.6
Married, %	88.8	89.1	89.3	90.6
Current smoker, %	57.2	54.9	52.8	49.7
Frequency of alcohol consumption				
Current drinker				
<1 time/week, %	2.6	3.6	5.0	5.9
1–2 time/week, %	5.1	6.3	7.3	7.8
3–4 time/week, %	9.1	10.1	10.7	10.3
almost daily, %	68.4	55.0	46.8	40.1
Former drinker, %	3.8	5.7	5.9	7.7
Nondrinker, %	9.5	17.0	21.1	24.0
Mean total energy intake, kcal/day (SD)	1,965 (507)	1,714 (482)	1,656 (490)	1,665 (466)

Table 3. Hazard ratios (HR) between three dietary patterns by factor score quartiles and esophageal cancer mortality

	Quartile of dietary patterns											
	Quartile 1	Quartile 2			Quartile 3			Quartile 4				*p* for trend
Vegetable pattern												
Person years	103,880	106,418			107,066			107,283				
Esophageal cancer cases, n	33	30			35			34				
Age-adjusted HR (95% CI)	1.00	0.81	(0.50 ,	1.34)	0.90	(0.56 ,	1.44)	0.81	(0.50 ,	1.31)		0.488
Multivariate HR (95% CI)[a]	1.00	0.77	(0.47 ,	1.27)	0.84	(0.51 ,	1.39)	0.81	(0.48 ,	1.36)		0.530
Animal food pattern												
Person years	104,287	105,586			107,046			107,728				
Esophageal cancer cases, n	22	43			28			39				
Age-adjusted HR (95% CI)	1.00	1.98	(1.18 ,	3.31)	1.28	(0.73 ,	2.24)	1.76	(1.04 ,	2.97)		0.175
Multivariate HR (95% CI)[a]	1.00	1.62	(0.96 ,	2.74)	0.98	(0.55 ,	1.75)	1.15	(0.65 ,	2.04)		0.746
Dairy product pattern												
Person years	107,209	107,021			107,317			103,100				
Esophageal cancer cases, n	57	36			17			22				
Age-adjusted HR (95% CI)	1.00	0.66	(0.44 ,	1.00)	0.32	(0.19 ,	0.55)	0.43	(0.26 ,	0.70)		< 0.001
Multivariate HR (95% CI)[a]	1.00	0.84	(0.54 ,	1.30)	0.47	(0.26 ,	0.83)	0.67	(0.38 ,	1.18)		0.042

[a]Adjusted for age, region, body mass index (BMI), education, smoking status, frequency of alcohol consumption, and total daily energy intake.

Table 4. Hazard ratios (HR) between three dietary patterns by factor score quartiles and esophageal cancer mortality by smoking status

	Quartile of dietary patterns											
	Quartile 1	Quartile 2			Quartile 3			Quartile 4			*p* for trend
Smoker											
Vegetable pattern											
Person years	74,733	72,043			68,599			64,605			
Esophageal cancer cases, n	28	28			25			29			
Age-adjusted HR (95% CI)	Reference	0.96	(0.57 ,	1.62)	0.86	(0.50 ,	1.48)	1.00	(0.59 ,	1.69)	0.907
Multivariate HR (95% CI)[a]	Reference	0.88	(0.52 ,	1.50)	0.77	(0.44 ,	1.34)	0.91	(0.51 ,	1.60)	0.653
Animal food pattern											
Person years	66,334	70,855			71,493			71,299			
Esophageal cancer cases, n	20	39			22			29			
Age-adjusted HR (95% CI)	Reference	1.84	(1.07 ,	3.15)	1.04	(0.57 ,	1.90)	1.35	(0.76 ,	2.38)	0.867
Multivariate HR (95% CI)[a]	Reference	1.50	(0.87 ,	2.60)	0.78	(0.42 ,	1.46)	0.84	(0.45 ,	1.56)	0.148
Dairy product pattern											
Person years	73,358	72,272			69,885			64,465			
Esophageal cancer cases, n	51	29			14			16			
Age-adjusted HR (95% CI)	Reference	0.61	(0.39 ,	0.97)	0.32	(0.18 ,	0.57)	0.39	(0.22 ,	0.68)	< 0.001
Multivariate HR (95% CI)[a]	Reference	0.76	(0.47 ,	1.23)	0.44	(0.23 ,	0.83)	0.57	(0.30 ,	1.09)	0.021
Nonsmoker											
Vegetable pattern											
Person years	29,146	34,375			38,467			42,678			
Esophageal cancer cases, n	5	2			10			5			
Age-adjusted HR (95% CI)	Reference	0.29	(0.06 ,	1.50)	1.18	(0.40 ,	3.47)	0.46	(0.13 ,	1.59)	0.582
Multivariate HR (95% CI)[a]	Reference	0.27	(0.05 ,	1.39)	0.99	(0.32 ,	3.06)	0.35	(0.09 ,	1.38)	0.388
Animal food pattern											
Person years	37,953	34,731			35,553			36,429			
Esophageal cancer cases, n	2	4			6			10			
Age-adjusted HR (95% CI)	Reference	2.44	(0.45 ,	13.33)	3.61	(0.73 ,	17.89)	6.10	(1.33 ,	27.91)	0.009
Multivariate HR (95% CI)[a]	Reference	2.57	(0.46 ,	14.38)	3.64	(0.69 ,	19.16)	6.01	(1.17 ,	30.88)	0.021
Dairy product pattern											
Person years	33,851	34,749			37,432			38,635			
Esophageal cancer cases, n	6	7			3			6			
Age-adjusted HR (95% CI)	Reference	1.12	(0.38 ,	3.34)	0.47	(0.12 ,	1.87)	0.91	(0.29 ,	2.83)	0.588
Multivariate HR (95% CI)[a]	Reference	1.35	(0.43 ,	4.23)	0.62	(0.14 ,	2.73)	1.27	(0.33 ,	4.85)	0.970

Smoker: current smoker and former smoker (quit <10 years ago). Nonsmoker: never smoker and former smoker (quit ≥10 years ago).

[a]Adjusted for age, region, body mass index (BMI), education, frequency of alcohol consumption, and total daily energy intake.