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Alcohol, Tobacco and Diet in Relation to Esophageal Cancer: The Shanghai Cohort Study

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Abstract

Prospective data on environmental exposures, especially with respect to alcohol, tobacco and diet, in relation to the risk of esophageal cancer in high risk populations are sparse. We analyzed data from a population-based cohort of 18 244 middle-aged and older men in Shanghai to identify risk factors for esophageal cancer in this high-risk population. The cohort was followed through 2006 and 101 incident esophageal cancer cases were identified. Cox proportional hazards models were used to estimate hazard ratios (HR) and their corresponding 95% confidence intervals (CI) for associations between exposures and esophageal cancer risk. With adjustment for tobacco use and other potential confounders, regular drinkers versus nondrinkers of alcoholic beverages had a 2-fold risk of developing esophageal cancer (HR = 2.02, 95% CI = 1.31–3.12). With adjustment for alcohol and other potential confounders, long-term smokers (40+ years) versus nonsmokers of cigarettes showed a 2-fold risk of developing esophageal cancer (HR=2.06, 95% CI=1.11–3.82). Increased consumption of fruits (including oranges/tangerines), seafood and milk were found to be protective against the development of esophageal cancer; HRs were decreased by 40%–60% for high versus low consumers after adjustment for cigarette smoking, alcohol drinking and other confounders.

Keywords

alcohol; tobacco; diet; esophageal cancer; Chinese

Introduction

Although esophageal cancer is rare in most western countries, the incidence varies greatly worldwide and is relatively high in Asia, southern and eastern Africa, and northwestern France (1). In high-risk regions such as Linxian in northern China, the incidence rate of esophageal cancer exceeds 100 per 100,000 persons per year. This malignancy exists in two main histological types, esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC), which are distinct in etiological and pathological characteristics. ESCC is the dominant histological type in high-incidence regions.

Alcohol consumption and tobacco smoking are established major risk factors for ESCC, especially in western populations (2,3). Many retrospective studies have demonstrated a synergistic effect of alcohol and smoking on ESCC risk (4–9). However, prospective studies on esophageal cancer, especially in high-incidence regions, are scarce and their results have been inconsistent (10–13). A cohort study in Linxian, China, found a weak association between smoking and ESCC but failed to detect statistically significant association with alcohol intake

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(13). The observed association between tobacco smoking and EAC risk is weaker than that for ESCC, and the effect of alcohol on EAC is uncertain (14–17).

Besides alcohol and tobacco, dietary factors may play a causal role in the carcinogenesis of esophageal cancer. Low intake of fresh fruits and vegetables, and a deficiency in antioxidants (e.g., β-carotene, vitamins C and E) have been found to be associated with elevated risk of esophageal cancer (18–25). Nitrosamines are considered carcinogenic and their presence in preserved foods such as salted fish, smoked meat and salted vegetables have been linked to increased risk of esophageal cancer (25). Previous studies have suggested that consumption of macronutrients such as protein and fat (21,26), as well as fresh fish (21) may be related to a reduced risk of ESCC.

There is little information from prospective studies on the possible roles of tobacco, alcohol and diet in esophageal cancer in high-risk populations. We examined the associations between these factors alone and in combination and risk of developing esophageal cancer in the Shanghai Cohort Study, which enrolled more than 18 000 middle-aged and older men during 1986–1989. In 1998 – 2002, the age-standardized incidence rates of esophageal cancer in men and women were 9.2 and 3.0 per 100,000, respectively (27), despite a marked decline in the incidence rate during the past 30 years (28).

Materials and Methods

Study population

Between January 1986 and September 1989, all eligible male residents of four small, geographically defined communities from a wide area of Shanghai City were invited to participate in a prospective, epidemiological study of diet and cancer. The eligibility criteria were 45–64 years of age and no history of cancer. During the 3-year recruitment period, 18 244 men, representing approximately 80% of eligible subjects, were enrolled in the study. The study was approved by the Institutional Review Boards of the University of Minnesota and the Shanghai Cancer Institute.

Baseline exposure assessment

At recruitment, a face-to-face interview was administered to each subject by a trained nurse. A structured questionnaire was used to collect subject's information on demographic characteristics (e.g., level of education, usual occupation, adult height and usual adult weight), history of tobacco and alcohol use, usual adult diet, and medical history.

For tobacco use, each participant was asked whether he had ever smoked at least one cigarette per day continuously for six months or longer. If he answered yes, he was further asked about the age at which he started to smoke cigarettes regularly, the average number of cigarettes smoked per day, and the number of years he had smoked. Information on the use of pipe was similarly collected. If the subject had quit smoking at enrollment, the age at which he stopped smoking was recorded.

For alcohol consumption, each participant was asked whether he had ever drunk alcoholic beverages at least once a week continuously for six months or longer. If the answer was yes, he was asked to provide the age at which he started to drink regularly and the usual amount of beer, rice wine, and spirits consumed separately. If the subject had quit his drinking habit at baseline interview, the age at which he stopped drinking was recorded. One alcoholic drink was defined as 360 g of beer (12.6 g of ethanol), 103 g of rice wine (12.5 g of ethanol), or 30 g of spirit (12.9 g of ethanol) (29).

To determine the level of consumption of specific foods or food groups, the subject was asked to indicate the frequency (in number of times per day, week, month, or year) with which he usually consumed each of 45 food items or food groups as an adult (the detailed information with the food list has been described elsewhere) (30). All common foods in the local diet were covered by these categories. For seasonal foods, we obtained the frequency of consumption when the food was in season.

Case ascertainment

Follow-up of cancer occurrence and death have been conducted through annual in-person re-interviews to all surviving cohort members and routine review of reports from the population-based Shanghai Cancer Registry and from the Shanghai Municipal Vital Statistics Office. Retired nurses employed by the Shanghai Cancer Institute visited the last known address of each surviving cohort member and updated the subject's medical history. For subjects who have moved, the new address was sought from neighbors or from the local police department. Follow-up on the cohort is almost complete. As of July 2006 (i.e., 20 years following cohort inception), only 769 (4.2%) cohort members were lost to follow-up.

As of July 2006, 101 esophageal cancer cases have been identified, including 68 ESCC cases, 8 EAC cases, 1 case with other and 24 with unknown histological types. Of the 68 ESCC cases, 62 cases were diagnosed based on histopathology, while the remaining 6 cases were based on cytology. All EAC cases were diagnosed based on histopathology.

Data analysis

For each individual, person-years of follow-up were counted from the date of recruitment to the date of cancer diagnosis or death, or the date of the last annual follow-up re-interview, whichever occurred first. Cox proportional hazards regression models were used to examine the associations between exposure variables and risk of esophageal cancer. Magnitude of the association was assessed by the hazard ratio (HR) and its 95% confidence interval (CI) and *P* value. All Cox regression models were adjusted for age at baseline interview, year of baseline interview, and neighborhood of residence at recruitment. The multivariate regression models included additional possible confounders as follows: level of education (no formal school or primary school, junior middle school, senior middle school, and college or above), body mass index (continuous), summed intakes of preserved food items in tertiles, fresh fruits in tertiles, and fresh vegetables in tertiles.

When we examined the main effect of alcohol on esophageal cancer risk, we further adjusted for the number of years of smoking (continuous), which was the single, independent predictor of esophageal cancer risk among all smoking variables under study. Conversely, when we assessed the main effect of smoking on esophageal cancer risk, we further adjusted for the number of drinks consumed per day (continuous) and the number of years of regular drinking (continuous), both of which independently predicted risk of esophageal cancer. The combined effect of smoking and alcohol drinking on risk was examined using a multiplicative proportional hazards regression model which included the following covariates: number of year of smoking (0, <40, 40+), number of drinks consumed per day (0, <4, 4+), and the cross-product of these two variables.

We performed statistical tests for linear trend on levels of smoking, alcohol drinking, and dietary factors by using ordinal scores for variables with more than 2 levels. Statistical computing was conducted using the SAS version 9.1 (SAS Institute Inc. Cary, NC) statistical software package. All *P* values quoted are two-sided. HRs with two-sided P values less than 0.05 were considered to be significantly different from 1.0.

Results

As of July 2006, 18 244 participants of the cohort had contributed 282 679 person-years of follow-up. One hundred and one incident cases of esophageal cancer had been identified, yielding an incidence rate of 35.7 per 100,000 person-years. Among esophageal cancer cases, the mean age at cancer diagnosis was 67.6 years (standard deviation= 7.3) and the mean time interval between entry into the study and cancer diagnosis was 10.2 years (range, 2 months to 19.1 years). Compared with subjects who remained free of esophageal cancer during the follow-up, esophageal cancer cases were less educated and had a significantly lower body mass index (mean, 21.6 vs. 22.2, $P = 0.02$). Of the 18 244 cohort members at baseline, 57.3% (n = 10 457) were ever smokers, and 42.6% (n = 7 773) consumed at least one alcoholic drink per week. Men who developed esophageal cancer were more likely to smoke cigarettes (76.2% vs. 57.2%) or consumed alcohol regularly (68.3% vs. 42.5%) compared with those who were free of esophageal cancer. Esophageal cancer patients began to smoke earlier in their lives (22.4 vs. 25.2, $P = 0.003$), had been smoking more years (33.2 vs. 29.6, $P = 0.003$), or had consumed more cigarettes over lifetime (29.6 vs. 25.0 pack-years, $P = 0.02$), but had similar number of cigarettes per day (17.2 vs. 16.2, $P = 0.27$). Relative to non-cases, esophageal cancer patients began drinking alcoholic beverages regularly at an earlier age (26.0 vs. 29.8 years, $P = 0.003$), drank for more years (31.2 vs. 25.9 years, $P = 0.001$), and consumed greater average amount per day (4.1 vs. 2.4 drinks, $P = 0.007$) (Table 1).

Table 2 shows the association between cigarette smoking and risk of esophageal cancer. The HR of esophageal cancer among ever compared to never smokers was 2.43 (95% CI = 1.53–3.84). The risk increased with younger age at starting to smoke, longer duration of smoking, increasing number of cigarettes per day and over lifetime (all P values for trend < 0.0001). After adjustment for alcohol intake and other potential confounders, all associations between cigarette smoking and risk of esophageal cancer were weaker, with age at starting to smoke (P for trend=0.04) and duration of smoking (P for trend=0.03) retaining their statistical significance (Table 2).

Table 3 shows the association between alcohol consumption and esophageal cancer risk. Compared to non-drinkers, men who consumed at least one drink a week for 6 months or longer had a HR of 2.74 (95% CI = 1.80–4.18). The risk increased with younger age at starting to drink regularly, longer duration of regular drinking, and increasing amounts of alcohol consumed daily and over lifetime (all P values for trend < 0.0001). The strong, graded, statistically significant positive association between alcohol intake and risk of esophageal cancer remained after adjustment for cigarette smoking and other potential confounders (Table 3).

We also examined the associations between types of alcoholic beverages and esophageal cancer risk. Spirits were most commonly consumed in the study population (54.5 % of total ethanol consumed by the study participants), followed by rice wine (33.1 % of total ethanol) and beer (12.4 % of total ethanol). Among regular drinkers, men who developed esophageal cancer consumed significantly more spirits per day than non-cases (3.2 vs. 1.3, $P = 0.004$). After adjustment for the consumption of rice wine and beer, smoking, and other factors, men who consumed 4 or more drinks of spirits per day had a HR of 4.93 (95% CI = 2.60–9.36) relative to non-drinkers (P for trend < 0.0001). Drinking rice wine also was associated with risk of esophageal cancer, but to a lesser extent than spirits (P for trend = 0.01). The association between beer consumption and risk of esophageal cancer in this study population was not statistically significant after adjustment for consumption of spirits, rice wine, smoking, and other factors (P for trend = 0.20) (Table 4).

Table 5 presents the combined effects of cigarette smoking and total alcohol consumption on risk of esophageal cancer. Smoking and alcohol drinking were highly correlated; 25.8% of heavy drinkers (4+ drinks per day) smoked cigarettes for more than 40 years, while only 14.2% of light drinkers (<4 drinks per day) and 8.1% of non-drinkers did so. At each level of smoking, risk of esophageal cancer increased with increasing number of alcoholic drinks consumed per day. The association of alcohol intake and esophageal cancer risk was stronger among smokers compared to non-smokers (*P* values for trend were 0.001 and 0.01 for smokers who smoked <40 years and 40+ years, respectively). Similarly, at each level of alcohol intake, risk of esophageal cancer increased with the number of years of smoking, although the tests for linear trend were not statistically significant. Highest risk was noted among subjects with the highest levels of tobacco and alcohol use. Compared to non-smokers and non-drinkers, subjects who smoked cigarettes for 40 years or longer and consumed 4 or more drinks per day had a HR of 8.00 (95% CI = 3.36–19.05).

Table 6 shows the association between consumption of various food items or groups and esophageal cancer risk. Significant protective effects were observed for intake of fresh fruits (*P* for trend < 0.0001) and intake of orange/tangerine (*P* for trend = 0.003). Subjects who drank milk (on average 5.5 times per week) were at a reduced risk for esophageal cancer compared to those who did not (HR = 0.44, 95% CI = 0.26–0.74). After adjustment for potential confounders, the inverse associations with intake of fresh fruits or orange/tangerine remained statistically significant or borderline significant (Table 6). The significant inverse association between intake of non-citrus fruits and esophageal cancer risk before adjustment (*P* for trend = 0.001) became statistically non-significant after adjustment (*P* for trend = 0.10). Adjustment for potential confounders strengthened the inverse association between intake of seafood products and risk of esophageal cancer (the *P* value for trend changed from 0.07 before adjustment to 0.04 following adjustment). The protective effect of milk on esophageal cancer development remained after adjustment for potential confounders (*P* = 0.056). After further adjustment for seafood intake and all other dietary variables listed in table 6 except for orange/tangerine, the inverse association between consumption of fresh fruits and risk of esophageal cancer remained borderline significant (*P* = 0.06).

Table 7 presents the association between intakes of macronutrients and risk of esophageal cancer. Significant inverse associations were noted for proteins (*P* for trend = 0.0003) and carbohydrates (*P* for trend = 0.01). The hazard ratios were 0.38 (95% CI = 0.22–0.65) and 0.51 (95% CI = 0.31–0.83) between subjects in the upper vs. lower tertiles of intakes of protein and carbohydrates, respectively. These inverse associations were no longer statistically significant after adjustment for potential confounders. Fat intake was not associated with risk of esophageal cancer in this study population.

We repeated the above analyses for the subset of ESCC cases (n = 68). After adjustment for alcohol consumption and other covariates, the HR of ESCC for those who smoked cigarettes for 40 years or longer relative to never smokers was 2.80 (95% CI = 1.26–6.20), with a statistically significant trend for risk in relation to number of years of smoking (*P* for trend = 0.014). Compared with non-drinkers, the multivariate adjusted HR for subjects who consumed 4 or more drinks a day was 4.64 (95% CI = 2.31–9.30). Dietary effects on ESCC were similar to those found for all esophageal cancer cases.

Discussion

In this prospective study, we demonstrated that alcohol consumption and cigarette smoking are independent risk factors for esophageal cancer in this historically high-risk population, while consumption of fresh fruits, orange/tangerine, seafood products and milk are protective factors.

The positive association between alcohol drinking and esophageal cancer risk has been reported in previous studies, mostly based on retrospective study design (4–11,31). These studies identified that amount of daily alcohol consumption, especially from hard liquor, had a strong effect on esophageal cancer risk. Our data also indicate that amount of alcohol consumed per day was significantly associated with elevated risk of this malignancy. The case-control study conducted in northern Italy reported that the ESCC risk was unaffected by duration of alcohol drinking (6). However, the present study found a significant association between duration of alcohol drinking and esophageal cancer risk. Results from case-control studies may be prone to recall bias, and the study participants might quit drinking due to early symptoms. The magnitude of the associations between alcohol intake and esophageal cancer risk in the present study is slightly stronger than that based on a retrospective case-control study conducted in the same population, suggesting the presence of recall bias in the latter study (8).

Although the exact mechanism by which alcohol causes esophageal cancer is unclear, several possible mechanistic pathways have been proposed: (i) Ethanol per se is not carcinogenic. However, its major intermediary metabolite, acetaldehyde, is a recognized animal carcinogen (32). (ii) Alcohol may act as a solvent which enhances the penetration of carcinogens from other environmental exposures (e.g., use of tobacco and consumption of nitrosamine containing foods) (32). (iii) Alcohol consumption may reduce the intake and bioavailability of certain nutrients, which may have chemo-preventive properties (e.g., antioxidants) (1,32). (iv) Alcohol may act as a direct irritant to the esophageal epithelium which gives rise to ESCC (1). Previous study found that higher concentration (40%) of ethanol could induce severe damage to the esophageal mucosa in rabbit, while lower ethanol concentration (20%) had much less adverse effect (33). In our cohort in Shanghai where ESCC was the major histological type, we identified a much higher relative risk for spirits than beer or rice wine intake. Thus the higher concentration of alcohol in spirits (43.0% of ethanol) than rice wine (12.1% of ethanol) or beer (3.5% of ethanol) may be the reason for the former's stronger association with esophageal cancer.

Tobacco is well-known to be carcinogenic in humans, and more than 60 carcinogens have been identified in tobacco smoke (34). Some of these compounds present in tobacco smoke and their *in vivo* metabolites could bind covalently to DNA, which consequently causes mutations in critical genes leading to carcinogenesis. In the United States and other western countries, tobacco is a major determinant of ESCC and the reported range of the relative risk among smokers was 2.0 – 5.0 (15,35). In the present study, after adjustment for alcohol intake and other potential confounders, we noted a roughly 50% increase in risk among current smokers and statistically significant inverse associations with age at starting to smoke and number of years of smoking. Furthermore, among non alcohol users, ever smokers exhibited a relative risk of 1.46 relative to never smokers. Therefore, although the relatively small sample size of cases in the present study preclude more definitive quantitative assessment of smoking as an independent risk factor for esophageal cancer, our overall data are consistent with this hypothesis. A cohort study in a high-risk Chinese population also reported a moderate effect of smoking on esophageal cancer (33% risk increase) (13).

Results of the present study support the hypothesis that constituents of fresh fruits (e.g., vitamin C, carotenoids, etc.) protect against esophageal cancer. Numerous studies have found an inverse relationship for consumption of fruits with esophageal cancer risk (13,21,22,25,36). In Shanghai, people rarely consume raw vegetables, thus the lack of a significant association between esophageal cancer and intake of vegetables in our study suggests that the protective components (e.g. vitamin C) in vegetables might have been greatly reduced by the high heat involved in stir-frying, the typical method of cooking in Shanghai. Our finding is consistent with other studies conducted in Chinese populations (13,37). Some reduction in esophageal cancer risk was associated with increased consumption of milk (the major diary product in the

local diet), as well as fresh fish and other seafood products, suggesting that poor overall nutrition may be linked to increased risk. Alternatively, specific components of these foods, such as n-3 polyunsaturated fatty acids in seafood and vitamin D in milk, may exert protective effects against esophageal cancer (21,38,39). In China, the prevalence of smoking and alcohol drinking actually has increased in recent decades (40,41). Therefore, we postulate that the substantial decline (more than 60% between 1972 and 1994) in esophageal cancer incidence among Shanghai males (28) is the result of better nutrition and increased availability of fresh fruits and other protective food groups in the local diet during the intervening years (25).

One limitation of the study is that women were not enrolled in this cohort and our hypotheses can only be assessed among men in Shanghai. However, there is no biological basis to speculate that the identified risk factors (alcohol, tobacco, diet) would not be applicable to women as well. Another limitation is the small number of cancer cases in this study. We lack sufficient statistical power to detect moderate main effects, or potential interaction effects between independent risk factors. Due to the extremely small number of EAC cases (n=8), we were unable to examine associations between exposures and EAC risk. Finally, despite careful attention to the issue of confounder adjustment, we cannot exclude the possibility of residual confounding in our risk estimation for alcohol, smoking, and diet. Heavy consumption of alcoholic beverages can interfere with the consumption and utilization of a variety of nutrients, while smokers are known to have low intake and circulating levels of antioxidants including carotenoids and vitamin C than nonsmokers (42,43).

Despite these limitations, the present study has several strengths. The strengths include the population-based study design, long duration of follow-up (up to 20 years), the almost complete ascertainment of incident cancer cases, and a study population at relatively high risk for esophageal cancer.

In summary, alcohol intake, tobacco use, and low consumption of fruits, seafood products and milk have been identified as risk factors for esophageal cancer in a high-risk population. These modifiable factors should be part of any primary prevention strategy for this human cancer with a very poor prognosis.

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References

1. Holmes RS, Vaughan TL. Epidemiology and pathogenesis of esophageal cancer. Semin Radiat Oncol 2007;17:2–9. [PubMed: 17185192]
2. International Agency for Research on Cancer. Alcohol drinking. Lyon; France: 1988.
3. International Agency for Research on Cancer. Tobacco smoking. Lyon; France: 1986.
4. Hashibe M, Boffetta P, Janout V, et al. Esophageal cancer in Central and Eastern Europe: tobacco and alcohol. Int J Cancer 2007;120:1518–1522. [PubMed: 17205526]
5. Lee CH, Lee JM, Wu DC, et al. Independent and combined effects of alcohol intake, tobacco smoking and betel quid chewing on the risk of esophageal cancer in Taiwan. Int J Cancer 2005;113:475–482. [PubMed: 15455377]
6. Zambon P, Talamini R, La Vecchia C, et al. Smoking, type of alcoholic beverage and squamous-cell oesophageal cancer in northern Italy. Int J Cancer 2000;86:144–149. [PubMed: 10728609]
7. Castellsague X, Munoz N, De Stefani E, et al. Independent and joint effects of tobacco smoking and alcohol drinking on the risk of esophageal cancer in men and women. Int J Cancer 1999;82:657–664. [PubMed: 10417762]

8. Gao YT, McLaughlin JK, Blot WJ, et al. Risk factors for esophageal cancer in Shanghai, China. I. Role of cigarette smoking and alcohol drinking. Int J Cancer 1994;58:192–196. [PubMed: 8026880]
9. Yu MC, Garabrant DH, Peters JM, Mack TM. Tobacco, alcohol, diet, occupation, and carcinoma of the esophagus. Cancer Res 1988;48:3843–3848. [PubMed: 3378219]
10. Kjaerheim K, Gaard M, Andersen A. The role of alcohol, tobacco, and dietary factors in upper aerogastric tract cancers: a prospective study of 10,900 Norwegian men. Cancer Causes Control 1998;9:99–108. [PubMed: 9486469]
11. Gronbaek M, Becker U, Johansen D, Tonnesen H, Jensen G, Sorensen TI. Population based cohort study of the association between alcohol intake and cancer of the upper digestive tract. BMJ 1998;317:844–847. [PubMed: 9748175]
12. Sakata K, Hoshiyama Y, Morioka S, Hashimoto T, Takeshita T, Tamakoshi A. Smoking, alcohol drinking and esophageal cancer: findings from the JACC Study. J Epidemiol 2005;15(Suppl 2):S212–219. [PubMed: 16127236]
13. Tran GD, Sun XD, Abnet CC, et al. Prospective study of risk factors for esophageal and gastric cancers in the Linxian general population trial cohort in China. Int J Cancer 2005;113:456–463. [PubMed: 15455378]
14. Lindblad M, Rodriguez LA, Lagergren J. Body mass, tobacco and alcohol and risk of esophageal, gastric cardia, and gastric non-cardia adenocarcinoma among men and women in a nested case-control study. Cancer Causes Control 2005;16:285–294. [PubMed: 15947880]
15. Gammon MD, Schoenberg JB, Ahsan H, et al. Tobacco, alcohol, and socioeconomic status and adenocarcinomas of the esophagus and gastric cardia. J Natl Cancer Inst 1997;89:1277–1284. [PubMed: 9293918]
16. Pera M, Manterola C, Vidal O, Grande L. Epidemiology of esophageal adenocarcinoma. J Surg Oncol 2005;92:151–159. [PubMed: 16299786]
17. Vaughan TL, Davis S, Kristal A, Thomas DB. Obesity, alcohol, and tobacco as risk factors for cancers of the esophagus and gastric cardia: adenocarcinoma versus squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev 1995;4:85–92. [PubMed: 7742727]
18. Cheng KK, Day NE. Nutrition and esophageal cancer. Cancer Causes Control 1996;7:33–40. [PubMed: 8850433]
19. Terry P, Lagergren J, Ye W, Nyren O, Wolk A. Antioxidants and cancers of the esophagus and gastric cardia. Int J Cancer 2000;87:750–754. [PubMed: 10925371]
20. De Stefani E, Brennan P, Boffetta P, Ronco AL, Mendilaharsu M, Deneo-Pellegrini H. Vegetables, fruits, related dietary antioxidants, and risk of squamous cell carcinoma of the esophagus: a case-control study in Uruguay. Nutr Cancer 2000;38:23–29. [PubMed: 11341040]
21. Launoy G, Milan C, Day NE, Pienkowski MP, Gignoux M, Faivre J. Diet and squamous-cell cancer of the oesophagus: a French multicentre case-control study. Int J Cancer 1998;76:7–12. [PubMed: 9533754]
22. Brown LM, Swanson CA, Gridley G, et al. Dietary factors and the risk of squamous cell esophageal cancer among black and white men in the United States. Cancer Causes Control 1998;9:467–474. [PubMed: 9934713]
23. Bollschweiler E, Wolfgarten E, Nowroth T, Rosendahl U, Monig SP, Holscher AH. Vitamin intake and risk of subtypes of esophageal cancer in Germany. J Cancer Res Clin Oncol 2002;128:575–580. [PubMed: 12384802]
24. Taylor PR, Qiao YL, Abnet CC, et al. Prospective study of serum vitamin E levels and esophageal and gastric cancers. J Natl Cancer Inst 2003;95:1414–1416. [PubMed: 13130117]
25. Gao YT, McLaughlin JK, Gridley G, et al. Risk factors for esophageal cancer in Shanghai, China. II. Role of diet and nutrients. Int J Cancer 1994;58:197–202. [PubMed: 8026881]
26. Franceschi S, Bidoli E, Negri E, et al. Role of macronutrients, vitamins and minerals in the aetiology of squamous-cell carcinoma of the oesophagus. Int J Cancer 2000;86:626–631. [PubMed: 10797282]
27. Cancer incidence in five continents. IX. Lyon; in press
28. Jin F, Devesa SS, Chow WH, et al. Cancer incidence trends in urban shanghai, 1972–1994: an update. Int J Cancer 1999;83:435–440. [PubMed: 10508476]

29. Adams, CF. Nutritive value of American foods in common units. Washington: Agricultural Research Service, U.S. Dept. of Agriculture: for sale by the Supt. of Docs., U.S. Govt. Print. Off; 1975. p. ivp. 291
30. Ross RK, Yuan JM, Henderson BE, Park J, Gao YT, Yu MC. Prospective evaluation of dietary and other predictors of fatal stroke in Shanghai, China. Circulation 1997;96:50–55. [PubMed: 9236416]
31. Castelletto R, Castellsague X, Munoz N, Iscovich J, Chopita N, Jmelnitsky A. Alcohol, tobacco, diet, mate drinking, and esophageal cancer in Argentina. Cancer Epidemiol Biomarkers Prev 1994;3:557–564. [PubMed: 7827585]
32. Blot WJ. Alcohol and cancer. Cancer Res 1992;52:2119s–2123s. [PubMed: 1544150]
33. Salo JA. Ethanol-induced mucosal injury in rabbit oesophagus. Scand J Gastroenterol 1983;18:713–721. [PubMed: 6669935]
34. International Agency for Research on Cancer. Tobacco smoke and involuntary smoking. Lyon; France: 2004.
35. Vineis P, Alavanja M, Buffler P, et al. Tobacco and cancer: recent epidemiological evidence. J Natl Cancer Inst 2004;96:99–106. [PubMed: 14734699]
36. Bosetti C, La Vecchia C, Talamini R, et al. Food groups and risk of squamous cell esophageal cancer in northern Italy. Int J Cancer 2000;87:289–294. [PubMed: 10861489]
37. Wu M, Zhao JK, Hu XS, et al. Association of smoking, alcohol drinking and dietary factors with esophageal cancer in high- and low-risk areas of Jiangsu Province, China. World J Gastroenterol 2006;12:1686–1693. [PubMed: 16586535]
38. Tavani A, Pelucchi C, Parpinel M, et al. n-3 polyunsaturated fatty acid intake and cancer risk in Italy and Switzerland. Int J Cancer 2003;105:113–116. [PubMed: 12672040]
39. Giovannucci E, Liu Y, Rimm EB, et al. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. J Natl Cancer Inst 2006;98:451–459. [PubMed: 16595781]
40. Yang G, Fan L, Tan J, et al. Smoking in China: findings of the 1996 National Prevalence Survey. JAMA 1999;282:1247–1253. [PubMed: 10517427]
41. Cochrane J, Chen H, Conigrave KM, Hao W. Alcohol use in China. Alcohol Alcohol 2003;38:537–542. [PubMed: 14633640]
42. Koh WP, Yuan JM, Sun CL, Lee HP, Yu MC. Middle-aged and older Chinese men and women in Singapore who smoke have less healthy diets and lifestyles than nonsmokers. J Nutr 2005;135:2473–2477. [PubMed: 16177215]
43. Yuan JM, Ross RK, Gao YT, Qu YH, Chu XD, Yu MC. Prediagnostic levels of serum micronutrients in relation to risk of gastric cancer in Shanghai, China. Cancer Epidemiol Biomarkers Prev 2004;13:1772–1780. [PubMed: 15533906]

Table 1

Baseline characteristics of the study population and esophageal cancer cases, the Shanghai Cohort Study 1986–2006

	Subjects who remained free of esophageal cancer (n=18,143)	Esophageal cancer cases (n=101)	2-sided *P*[*]
Age at interview			
Mean (SD)	55.3 (5.7)	56.9 (5.4)	0.004
<50 (%)	3471 (19.1)	11 (10.9)	0.002
50 – <55	4371 (24.1)	19 (18.8)	
55 – <60	5292 (29.2)	31 (30.7)	
60+	5009 (27.6)	40 (39.6)	
Height (cm)			
Mean (SD)	168.7 (5.5)	168.7 (5.5)	0.95
Weight (kg)			
Mean (SD)	63.1 (9.1)	61.5 (8.2)	0.07
Body mass index (kg/m^2)			
Mean (SD)	22.2 (3.0)	21.6 (2.5)	0.02
<18.5 (%)	1749 (9.6)	12 (11.9)	0.11
18.5 - <21.0	5107 (28.2)	26 (25.7)	
21.0 - <23.5	5378 (29.6)	42 (41.6)	
23.5 - <26.0	3865 (21.3)	14 (13.9)	
26.0+	2044 (11.3)	7 (6.9)	
Level of education (%)			
No formal school or primary school	5146 (28.4)	54 (53.5)	<0.0001
Junior middle school	5301 (29.2)	29 (28.7)	
Senior middle school	3193 (17.6)	12 (11.9)	
College or above	453 (24.8)	6 (5.9)	
Cigarette smoking (%)			
Never	7763 (42.8)	24 (23.8)	<0.0001
Ever	10380 (57.2)	77 (76.2)	
Former smokers	1252 (6.9)	4 (4.0)	
Current smokers	9128 (50.3)	73 (72.3)	
Among smokers (Mean (SD))	(n = 10380)	(n = 77)	
Age at starting to smoke	25.2 (8.5)	22.4 (7.3)	0.003
No. years of smoking	29.6 (10.7)	33.2 (11.1)	0.003
No. cigarettes per day	16.2 (8.2)	17.2 (7.9)	0.27
No. pack-years of cigarettes [†]	25.0 (16.6)	29.6 (17.2)	0.02
Regular alcohol drinking (%)			
Never	10439 (57.5)	32 (31.7)	<0.0001
Ever	7704 (42.5)	69 (68.3)	
Among drinkers (Mean (SD))	(n = 7704)	(n = 69)	
Age at starting to drink regularly	29.8 (12.2)	26.0 (10.1)	0.003
No. years of drinking	25.9 (13.1)	31.2 (12.0)	0.001
No. drinks of alcoholic beverages/day	2.4 (2.4)	4.1 (5.0)	0.007
Daily ethanol intake (g)	30.5 (30.6)	52.3 (65.1)	0.007
Lifetime ethanol intake (kg)	321.0 (412.1)	657.9 (1131.1)	0.02

[*] t-test for continuous variables and chi-square test for categorical variables

[†] One pack-year equals to 20 cigarettes (one pack) per day for one year.

Table 2

Cigarette smoking in relation to hazard ratio of esophageal cancer, the Shanghai Cohort Study 1986–2006

	Person-years	Number of Cases (n=101)	HR(95% CI)*	Adjusted HR† (95% CI)
Smoking Status				
Never smokers	123,359	24	1.00	1.00
Ever smokers	159,320	77	2.43 (1.53, 3.84)	1.36 (0.83, 2.21)
Former smokers	18,273	4	0.94 (0.32, 2.71)	0.62 (0.21, 1.80)
Current smokers	141,047	73	2.66 (1.67, 4.21)	1.46 (0.89, 2.39)
Age at starting to smoke				
Never smokers	123,359	24	1.00	1.00
25+	72,516	21	1.51 (0.84, 2.71)	1.02 (0.56, 1.86)
20–24	51,713	29	2.80 (1.63, 4.81)	1.56 (0.88, 2.75)
< 20	35,091	27	3.69 (2.12, 6.41)	1.72 (0.95, 3.12)
P for trend			<0.0001	0.04
No. years of smoking				
Never smokers	123,359	24	1.00	1.00
<40	130,728	48	1.94 (1.19, 3.18)	1.17 (0.70, 1.96)
40+	28,592	29	4.29 (2.40, 7.67)	2.06 (1.11, 3.82)
P for trend			<0.0001	0.03
No. cigarettes per day				
Never smokers	123,359	24	1.00	1.00
<20	81,171	31	1.95 (1.15, 3.33)	1.26 (0.73, 2.18)
20+	78,149	46	2.91 (1.77, 4.77)	1.45 (0.85, 2.47)
P for trend			<0.0001	0.17
No. pack-years of cigarettes‡				
Never smokers	123,359	24	1.00	1.00
<30	105,866	41	2.07 (1.25, 3.43)	1.33 (0.79, 2.23)
30–59	47,834	31	2.95 (1.72, 5.06)	1.40 (0.79, 2.48)
60+	5,620	5	3.84 (1.46, 10.14)	1.49 (0.54, 4.07)
P for trend			<0.0001	0.26

*Hazard ratios (HRs) were calculated using Cox proportional hazards regression models, which included covariates for age at interview, year of interview, and neighborhood of residence at recruitment; CI, confidence interval

†Hazard ratios were further adjusted for level of education, body mass index, number of drinks consumed per day, number of years of drinking, and summed intakes of preserved food items (in tertiles), fresh fruits (in tertiles) and fresh vegetables (in tertiles).

‡One pack-year equals to 20 cigarettes (one pack) per day for one year.

Table 3

Consumption of alcoholic beverages in relation to hazard ratio of esophageal cancer, the Shanghai Cohort Study 1986–2006

	Person-years	Number of Cases (n=101)	HR (95% CI) *	Adjusted HR† (95% CI)
Drinking status				
Non-drinkers	162,184	32	1.00	1.00
Regular drinkers	120,495	69	2.74 (1.80, 4.18)	2.02 (1.31, 3.12)
Age at starting to drink regularly				
Non-drinkers	162,184	32	1.00	1.00
30+	55,577	23	1.97 (1.15, 3.38)	1.58 (0.92, 2.71)
20–29	45,282	30	3.25 (1.97, 5.35)	2.37 (1.41, 3.98)
< 20	19,636	16	3.80 (2.08, 6.95)	2.54 (1.36, 4.74)
P for trend			<0.0001	0.0003
No. years of drinking regularly				
Non-drinkers	162,184	32	1.00	1.00
< 20	38,067	12	1.60 (0.82, 3.11)	1.33 (0.68, 2.59)
20–39	63,128	35	2.77 (1.71, 4.48)	2.02 (1.23, 3.32)
40+	19,300	22	4.63 (2.60, 8.22)	3.22 (1.77, 5.86)
P for trend			<0.0001	<0.0001
No. drinks of alcoholic beverages per day				
Non-drinkers	162,184	32	1.00	1.00
< 1	38,996	11	1.39 (0.70, 2.77)	1.22 (0.62, 2.44)
1 - <2	29,398	14	2.30 (1.22, 4.31)	1.87 (0.99, 3.53)
2 - <4	32,991	20	2.84 (1.62, 4.98)	2.01 (1.13, 3.59)
4+	19,110	24	5.98 (3.51, 10.19)	3.74 (2.12, 6.59)
P for trend			<0.0001	<0.0001
Daily ethanol intake (g)				
Non-drinkers	162,184	32	1.00	1.00
<20	57,149	19	1.64 (0.93, 2.90)	1.42 (0.81, 2.52)
20 - <40	30,326	14	2.18 (1.16, 4.10)	1.67 (0.88, 3.18)
40 - <80	25,678	24	4.39 (2.58, 7.47)	2.88 (1.64, 5.06)
80+	7,342	12	7.78 (3.99, 15.16)	4.65 (2.31, 9.36)
P for trend			<0.0001	<0.0001
Lifetime ethanol intake (kg)				
Non-drinkers	162,184	32	1.00	1.00
<300	78,545	32	2.03 (1.24, 3.31)	1.69 (1.03, 2.77)
300 - <800	31,437	20	2.96 (1.69, 5.19)	2.00 (1.11, 3.59)
800+	10,513	17	7.12 (3.92, 12.94)	4.26 (2.26, 8.01)
P for trend			<0.0001	<0.0001

* Hazard ratios (HRs) were calculated using Cox proportional hazards regression models, which included covariates for age at interview, year of interview, and neighborhood of residence at recruitment; CI, confidence interval.

† Hazard ratios were further adjusted for level of education, body mass index, number of years of smoking, and summed intakes of preserved food items (in tertiles), fresh fruits (in tertiles) and fresh vegetables (in tertiles).

Table 4

Consumption of different types of alcoholic beverages in relation to hazard ratio of esophageal cancer, the Shanghai Cohort Study 1986–2006

Type of alcohol (drink/day)	Person-years	Number of Cases	HR (95% CI) *	Adjusted HR† (95% CI)
Non-drinkers	162,184	32	1.00	1.00
Beer‡				
< 1	41,697	15	1.83 (0.99, 3.38)	1.46 (0.75, 2.85)
1+	13,403	7	2.58 (1.14, 5.85)	1.71 (0.66, 4.42)
P for trend			0.007	0.20
Rice wine§				
< 1	33,301	10	1.51 (0.74, 3.07)	1.39 (0.66, 2.90)
1 - <2	15,261	12	3.92 (2.01, 7.65)	3.51 (1.73, 7.13)
2+	18,731	9	2.29 (1.09, 4.81)	1.82 (0.82, 4.01)
P for trend			0.0005	0.01
Spirits¶				
< 2	30,544	8	1.25 (0.57, 2.71)	1.02 (0.45, 2.30)
2 - <4	16,528	15	4.28 (2.31, 7.94)	2.87 (1.48, 5.58)
4+	10,451	18	8.22 (4.59, 14.73)	4.93 (2.60, 9.36)
P for trend			<0.0001	<0.0001

* Hazard ratios (HRs) were calculated using Cox proportional hazards regression models, which included covariates for age at interview, year of interview, and neighborhood of residence at recruitment; CI, confidence interval.

† Hazard ratios were further adjusted for level of education, body mass index, number of years of smoking, and summed intakes of preserved food items (in tertiles), fresh fruits (in tertiles) and fresh vegetables (in tertiles).

‡ Subjects who consumed rice wine and/or spirits only were excluded from this analysis; hazard ratios were further adjusted for consumption of rice wine and spirits.

§ Subjects who consumed beer and/or spirits only were excluded from this analysis; hazard ratios were further adjusted for consumption of beer and spirits.

¶ Subjects who consumed beer and/or rice wine only were excluded from this analysis; hazard ratios were further adjusted for consumption of beer and rice wine.

Table 5

Joint effect of alcohol drinking and cigarette smoking on risk of esophageal cancer, the Shanghai Cohort Study 1986–2006

Number of years of smoking		Number of drinks per day			*P* for trend
		Non-drinkers	<4	4+	
Non-smokers	**Cases**	13	9	2	
	Person-years	90151	30668	2540	
	HR* **(95% CI)**	1.00	1.75 (0.75–4.11)	3.86 (0.86–17.26)	0.12
<40	**Cases**	13	23	12	
	Person-years	60719	57932	12076	
	HR* **(95% CI)**	1.26 (0.58–2.73)	2.01 (1.00–4.01)	4.55 (2.03–10.18)	0.001
40+	**Cases**	6	13	10	
	Person-years	11313	12785	4494	
	HR* **(95% CI)**	2.18 (0.80–5.92)	4.13 (1.85–9.25)	8.00 (3.36–19.05)†	0.01
***P* for trend**		0.18	0.11	0.10	

*Hazard ratios (HRs) were calculated using Cox proportional hazards regression models, which included covariates for age at interview, year of interview, neighborhood of residence at recruitment, body mass index, level of education, and summed intakes of preserved food items (in tertiles), fresh fruits (in tertiles) and fresh vegetables (in tertiles).

†2-sided *P* for interaction = 0.99

Table 6

Consumption of selected food items/groups in relation to hazard ratio of esophageal cancer, the Shanghai Cohort Study 1986–2006

Food items or groups		Level of consumption in tertile			*P* for trend
		1 (lowest)	2	3 (highest)	
Fresh fruits	HR (95% CI)*	1.00	0.53 (0.35, 0.82)	0.29 (0.15, 0.54)	<0.0001
	Adj. HR† (95% CI)	1.00	0.70 (0.45, 1.09)	0.46 (0.25, 0.88)	0.01
Orange/tangerine	HR (95% CI)*	1.00	0.65 (0.42, 1.00)	0.41 (0.22, 0.78)	0.003
	Adj. HR† (95% CI)	1.00	0.80 (0.52, 1.23)	0.56 (0.30, 1.05)	0.06
Fresh vegetables	HR (95% CI)*	1.00	0.82 (0.29, 2.32)	0.72 (0.26, 1.98)	0.43
	Adj. HR† (95% CI)	1.00	0.83 (0.29, 2.36)	0.71 (0.26, 1.95)	0.34
Meat	HR (95% CI)*	1.00	0.99 (0.63, 1.56)	0.77 (0.47, 1.27)	0.31
	Adj. HR† (95% CI)	1.00	1.04 (0.66, 1.64)	0.81 (0.49, 1.34)	0.43
Fish and seafood products	HR (95% CI)*	1.00	1.05 (0.66, 1.67)	0.64 (0.39, 1.05)	0.07
	Adj. HR† (95% CI)	1.00	1.07 (0.67, 1.70)	0.59 (0.36, 0.97)	0.04
Egg	HR (95% CI)*	1.00	0.48 (0.30, 0.77)	0.70 (0.43, 1.13)	0.12
	Adj. HR† (95% CI)	1.00	0.53 (0.33, 0.85)	0.83 (0.51, 1.35)	0.36
Milk‡	HR (95% CI)*	1.00	0.44 (0.26, 0.74)	-	-
	Adj. HR† (95% CI)	1.00	0.59 (0.35, 1.01)	-	-
Preserved foods	HR (95% CI)*	1.00	1.07 (0.66, 1.73)	1.01 (0.62, 1.63)	0.99
	Adj. HR† (95% CI)	1.00	0.99 (0.61, 1.61)	0.94 (0.58, 1.52)	0.79

*Hazard ratios (HRs) were calculated using Cox proportional hazards regression models, which included covariates for age at interview, year of interview, neighborhood of residence at recruitment.

†Hazard ratios (HRs) were further adjusted for level of education, body mass index, number of years of smoking, number of drinks consumed per day, and number of years of drinking.

‡The average intake of milk was 5.5 times per week for those who reported “ever consumed”, and it was compared to nondrinkers of milk.

Table 7

Consumption of macronutrients from foods in relation to hazard ratio of esophageal cancer, the Shanghai Cohort Study 1986–2006

Nutrients		Level of consumption in tertile			*P* for trend
		1 (lowest)	2	3 (highest)	
Protein	HR (95% CI)*	1.00	0.42 (0.25, 0.70)	0.38 (0.22, 0.65)	0.0003
	Adj. HR† (95% CI)	1.00	0.58 (0.35, 0.97)	0.72 (0.41, 1.26)	0.20
Fat	HR (95% CI)*	1.00	1.05 (0.62, 1.77)	0.62 (0.32, 1.19)	0.08
	Adj. HR† (95% CI)	1.00	1.40 (0.83, 2.36)	1.21 (0.63, 2.31)	0.55
Carbohydrates	HR (95% CI)*	1.00	0.58 (0.36, 0.94)	0.51 (0.31, 0.83)	0.01
	Adj. HR† (95% CI)	1.00	0.76 (0.47, 1.24)	0.90 (0.53, 1.51)	0.61

*Hazard ratios (HRs) were calculated using Cox proportional hazards regression models, which included covariates for age at interview, year of interview, neighborhood of residence at recruitment.

†Hazard ratios (HRs) were further adjusted for level of education, body mass index, number of years of smoking, number of drinks consumed per day, and number of years of drinking.