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

Yunhua Fan, Jian-Min Yuan, and Renwei Wang
The Cancer Center, University of Minnesota, Minneapolis, Minnesota, USA

Yu-Tang Gao
Department of Epidemiology, Shanghai Cancer Institute, Shanghai, People’s Republic of China

Mimi C. Yu
The Cancer Center, University of Minnesota, Minneapolis, Minnesota, USA

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 vs. nondrinkers of alcoholic beverages had a twofold 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+ yr) vs. nonsmokers of cigarettes showed a twofold 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 vs. low consumers after adjustment for cigarette smoking, alcohol drinking, and other confounders.

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 yr. This malignancy exists in 2 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 (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 the risk of developing esophageal cancer in the Shanghai Cohort Study, which enrolled more than 18,000 middle-aged and older men during 1986–89. 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 4 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 to 64 yr of age and no history of cancer. During the 3-yr 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 subjects’ 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 subject was asked whether he had ever smoked at least 1 cigarette per day continuously for 6 mo 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 a 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 subject was asked whether he had ever drunk alcoholic beverages at least once a week continuously for 6 mo 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 reinterviews 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 had 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 yr 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, whereas 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 reinterview, 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 that included the following covariates: number of years of smoking (0, <40, 40+), number of drinks consumed per day (0, <4, 4+), and the cross-product of these 2 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 2-sided. HRs with 2-sided P values less than 0.05 were considered to be significantly different from 1.0.
RESULTS
As of July 2006, 18,244 subjects of the cohort had contributed 282,679 person yr of follow-up. A total of 101 incident cases of esophageal cancer had been identified, yielding an incidence rate of 35.7 per 100,000 person yr. Among esophageal cancer cases, the mean age at cancer diagnosis was 67.6 yr (SD = 7.3) and the mean time interval between entry into the study and cancer diagnosis was 10.2 yr (range, 2 mo to 19.1 yr). 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 1 alcoholic drink per wk. 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 a lifetime (29.6 vs. 25.0 pack yr, P = 0.02) but had similar number of cigarettes per day (17.2 vs. 16.2, P = 0.27). Relative to noncases, esophageal cancer patients began drinking alcoholic beverages regularly at an earlier age (26.0 vs. 29.8 yr, P = 0.003), drank for more years (31.2 vs. 25.9 yr, 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 nondrinkers, men who consumed at least 1 drink a wk for 6 mo or longer had an 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 subjects) 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 noncases (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 nondrinkers (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. Drinking and alcohol drinking were highly correlated; 25.8% of heavy drinkers (4+ drinks per day) smoked cigarettes for more than 40 yr, whereas only 14.2% of light drinkers (<4 drinks per day) and 8.1% of nondrinkers 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 nonsmokers (P values for trend were 0.001 and 0.01 for smokers who smoked <40 yr and 40+ yr, 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 nonsmokers and nondrinkers, subjects who smoked cigarettes for 40 yr 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/wk) 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 noncitrus fruits and esophageal cancer risk before adjustment (P for trend = 0.001) became statistically nonsignificant 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
# Table 1
Baseline characteristics of the study population and esophageal cancer cases, the Shanghai cohort study, 1986–2006

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Subjects who remained free of esophageal cancer ($n = 18,143$)</th>
<th>Esophageal cancer cases ($n = 101$)</th>
<th>2-sided $P^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at interview (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>55.3 (5.7)</td>
<td>56.9 (5.4)</td>
<td>0.004</td>
</tr>
<tr>
<td>&lt;50 (%)</td>
<td>3,471 (19.1)</td>
<td>11 (10.9)</td>
<td>0.002</td>
</tr>
<tr>
<td>50 – &lt;55</td>
<td>4,371 (24.1)</td>
<td>19 (18.8)</td>
<td></td>
</tr>
<tr>
<td>55 – &lt;60</td>
<td>5,292 (29.2)</td>
<td>31 (30.7)</td>
<td></td>
</tr>
<tr>
<td>60 +</td>
<td>5,009 (27.6)</td>
<td>40 (39.6)</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>168.7 (5.5)</td>
<td>168.7 (5.5)</td>
<td>0.95</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>63.1 (9.1)</td>
<td>61.5 (8.2)</td>
<td>0.07</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>22.2 (3.0)</td>
<td>21.6 (2.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>&lt;18.5 (%)</td>
<td>1,749 (9.6)</td>
<td>12 (11.9)</td>
<td>0.11</td>
</tr>
<tr>
<td>18.5 – &lt;21.0</td>
<td>5,107 (28.2)</td>
<td>26 (25.7)</td>
<td></td>
</tr>
<tr>
<td>21.0 – &lt;23.5</td>
<td>5,378 (29.6)</td>
<td>42 (41.6)</td>
<td></td>
</tr>
<tr>
<td>23.5 – &lt;26.0</td>
<td>3,865 (21.3)</td>
<td>14 (13.9)</td>
<td></td>
</tr>
<tr>
<td>26.0 +</td>
<td>2,044 (11.3)</td>
<td>7 (6.9)</td>
<td></td>
</tr>
<tr>
<td>Level of education (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No formal school or primary school</td>
<td>5,146 (28.4)</td>
<td>54 (53.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Junior middle school</td>
<td>5,301 (29.2)</td>
<td>29 (28.7)</td>
<td></td>
</tr>
<tr>
<td>Senior middle school</td>
<td>3,193 (17.6)</td>
<td>12 (11.9)</td>
<td></td>
</tr>
<tr>
<td>College or above</td>
<td>453 (24.8)</td>
<td>6 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>7,763 (42.8)</td>
<td>24 (23.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ever</td>
<td>10,380 (57.2)</td>
<td>77 (76.2)</td>
<td></td>
</tr>
<tr>
<td>Former smokers</td>
<td>1,252 (6.9)</td>
<td>4 (4.0)</td>
<td></td>
</tr>
<tr>
<td>Current smokers</td>
<td>9,128 (50.3)</td>
<td>73 (72.3)</td>
<td></td>
</tr>
<tr>
<td>Among smokers, mean (SD)</td>
<td>10,380</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>Age at starting to smoke (yr)</td>
<td>25.2 (8.5)</td>
<td>22.4 (7.3)</td>
<td>0.003</td>
</tr>
<tr>
<td>No. yr of smoking</td>
<td>29.6 (10.7)</td>
<td>33.2 (11.1)</td>
<td>0.003</td>
</tr>
<tr>
<td>No. cigarettes per day</td>
<td>16.2 (8.2)</td>
<td>17.2 (7.9)</td>
<td>0.27</td>
</tr>
<tr>
<td>No. pack years of cigarettes$^b$</td>
<td>25.0 (16.6)</td>
<td>29.6 (17.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Regular alcohol drinking (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>10,439 (57.5)</td>
<td>32 (31.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ever</td>
<td>10,704 (56.7)</td>
<td>69 (68.3)</td>
<td></td>
</tr>
<tr>
<td>Among drinkers, mean (SD)</td>
<td>7,704</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>Age at starting to drink regularly (yr)</td>
<td>29.8 (12.2)</td>
<td>26.0 (10.1)</td>
<td>0.003</td>
</tr>
<tr>
<td>No. yr of drinking</td>
<td>25.9 (13.1)</td>
<td>31.2 (12.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>No. drinks of alcoholic beverages/day</td>
<td>2.4 (2.4)</td>
<td>4.1 (5.0)</td>
<td>0.007</td>
</tr>
<tr>
<td>Daily ethanol intake (g)</td>
<td>30.5 (30.6)</td>
<td>52.3 (65.1)</td>
<td>0.007</td>
</tr>
<tr>
<td>Lifetime ethanol intake (kg)</td>
<td>321.0 (412.1)</td>
<td>657.9 (1,131.1)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

$^a$ t-test for continuous variables and chi-square test for categorical variables.

$^b$ 1 pack yr equals to 20 cigarettes (1 pack) per day for 1 yr.

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.
Cigarette smoking in relation to hazard ratio of esophageal cancer, the Shanghai cohort study, 1986–2006

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Person years</th>
<th>No. of cases (n = 101)</th>
<th>HR (95% CI)a</th>
<th>Adjusted HRb (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smokers</td>
<td>123,359</td>
<td>24</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Ever smokers</td>
<td>159,320</td>
<td>77</td>
<td>2.43 (1.53–3.84)</td>
<td>1.36 (0.83–2.21)</td>
</tr>
<tr>
<td>Former smokers</td>
<td>18,273</td>
<td>4</td>
<td>0.94 (0.32–2.71)</td>
<td>0.62 (0.21–1.80)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>141,047</td>
<td>73</td>
<td>2.66 (1.67–4.21)</td>
<td>1.46 (0.89–2.39)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age at starting to smoke</th>
<th>Person years</th>
<th>No. of cases (n = 101)</th>
<th>HR (95% CI)a</th>
<th>Adjusted HRb (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smokers</td>
<td>123,359</td>
<td>24</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>25+</td>
<td>72,516</td>
<td>21</td>
<td>1.51 (0.84–2.71)</td>
<td>1.02 (0.56–1.86)</td>
</tr>
<tr>
<td>20–24</td>
<td>51,713</td>
<td>29</td>
<td>2.80 (1.63–4.81)</td>
<td>1.56 (0.88–2.75)</td>
</tr>
<tr>
<td>&lt;20</td>
<td>35,091</td>
<td>27</td>
<td>3.69 (2.12–6.41)</td>
<td>1.72 (0.95–3.12)</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td>&lt;0.0001</td>
<td></td>
<td>0.04</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. yr of smoking</th>
<th>Person years</th>
<th>No. of cases (n = 101)</th>
<th>HR (95% CI)a</th>
<th>Adjusted HRb (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smokers</td>
<td>123,359</td>
<td>24</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>&lt;40</td>
<td>130,728</td>
<td>48</td>
<td>1.94 (1.19–3.18)</td>
<td>1.17 (0.70–1.96)</td>
</tr>
<tr>
<td>40+</td>
<td>28,592</td>
<td>29</td>
<td>4.29 (2.40–7.67)</td>
<td>2.06 (1.11–3.82)</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td>&lt;0.0001</td>
<td></td>
<td>0.03</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. cigarettes per day</th>
<th>Person years</th>
<th>No. of cases (n = 101)</th>
<th>HR (95% CI)a</th>
<th>Adjusted HRb (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smokers</td>
<td>123,359</td>
<td>24</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>&lt;20</td>
<td>81,171</td>
<td>31</td>
<td>1.95 (1.15–3.33)</td>
<td>1.26 (0.73–2.18)</td>
</tr>
<tr>
<td>20+</td>
<td>78,149</td>
<td>46</td>
<td>2.91 (1.77–4.77)</td>
<td>1.45 (0.85–2.47)</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td>&lt;0.0001</td>
<td></td>
<td>0.17</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. pack years of cigarettesc</th>
<th>Person years</th>
<th>No. of cases (n = 101)</th>
<th>HR (95% CI)a</th>
<th>Adjusted HRb (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smokers</td>
<td>123,359</td>
<td>24</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>&lt;30</td>
<td>105,866</td>
<td>41</td>
<td>2.07 (1.25–3.43)</td>
<td>1.33 (0.79–2.23)</td>
</tr>
<tr>
<td>30–59</td>
<td>47,834</td>
<td>31</td>
<td>2.95 (1.72–5.06)</td>
<td>1.40 (0.79–2.48)</td>
</tr>
<tr>
<td>60+</td>
<td>5,620</td>
<td>5</td>
<td>3.84 (1.46–10.14)</td>
<td>1.49 (0.54–4.07)</td>
</tr>
<tr>
<td>P for trend</td>
<td></td>
<td>&lt;0.0001</td>
<td></td>
<td>0.26</td>
</tr>
</tbody>
</table>

Abbreviations are as follows: HR, hazard ratios; CI, confidence interval. 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.

HRs 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).

1 pack yr equals to 20 cigarettes (1 pack) per day for 1 yr.

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, whereas 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 have 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, in this study, we 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 subjects might quit drinking due to early symptoms. The magnitude of the
TABLE 3
Consumption of alcoholic beverages in relation to hazard ratio of esophageal cancer, the Shanghai cohort study, 1986–2006

<table>
<thead>
<tr>
<th>Drinking status</th>
<th>Person years</th>
<th>No. of Cases (n = 101)</th>
<th>HR (95% CI)</th>
<th>Adjusted HR(b) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondrinkers</td>
<td>162,184</td>
<td>32</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Regular drinkers</td>
<td>120,495</td>
<td>69</td>
<td>2.74 (1.80–4.18)</td>
<td>2.02 (1.31–3.12)</td>
</tr>
</tbody>
</table>

Age at starting to drink regularly

<table>
<thead>
<tr>
<th>Age at starting</th>
<th>Person years</th>
<th>No. of Cases (n = 101)</th>
<th>HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondrinkers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30+</td>
<td>162,184</td>
<td>32</td>
<td>1.97 (1.15–3.38)</td>
<td>1.58 (0.92–2.71)</td>
</tr>
<tr>
<td>20–29</td>
<td>55,577</td>
<td>23</td>
<td>3.25 (1.97–5.35)</td>
<td>2.37 (1.41–3.98)</td>
</tr>
<tr>
<td>&lt;20</td>
<td>19,636</td>
<td>16</td>
<td>3.80 (2.08–6.95)</td>
<td>2.54 (1.36–4.74)</td>
</tr>
<tr>
<td>(P) for trend</td>
<td>(&lt;0.0001)</td>
<td>(&lt;0.0001)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No. yr of drinking regularly

<table>
<thead>
<tr>
<th>No. yr of drinking</th>
<th>Person years</th>
<th>No. of Cases (n = 101)</th>
<th>HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondrinkers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>162,184</td>
<td>32</td>
<td>1.60 (0.82–3.11)</td>
<td>1.33 (0.68–2.59)</td>
</tr>
<tr>
<td>20–39</td>
<td>63,128</td>
<td>35</td>
<td>2.77 (1.71–4.48)</td>
<td>2.02 (1.23–3.32)</td>
</tr>
<tr>
<td>40+</td>
<td>19,300</td>
<td>22</td>
<td>4.63 (2.60–8.22)</td>
<td>3.22 (1.77–5.86)</td>
</tr>
<tr>
<td>(P) for trend</td>
<td>(&lt;0.0001)</td>
<td>(&lt;0.0001)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No. drinks of alcoholic beverages per day

<table>
<thead>
<tr>
<th>No. drinks of beverages</th>
<th>Person years</th>
<th>No. of Cases (n = 101)</th>
<th>HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondrinkers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>162,184</td>
<td>32</td>
<td>1.39 (0.70–2.77)</td>
<td>1.22 (0.62–2.44)</td>
</tr>
<tr>
<td>1 – &lt;2</td>
<td>29,398</td>
<td>14</td>
<td>2.30 (1.22–4.31)</td>
<td>1.87 (0.99–3.53)</td>
</tr>
<tr>
<td>2 – &lt;4</td>
<td>32,991</td>
<td>20</td>
<td>2.84 (1.62–4.98)</td>
<td>2.01 (1.13–3.59)</td>
</tr>
<tr>
<td>4 +</td>
<td>19,110</td>
<td>24</td>
<td>5.98 (3.51–10.19)</td>
<td>3.74 (2.12–6.59)</td>
</tr>
<tr>
<td>(P) for trend</td>
<td>(&lt;0.0001)</td>
<td>(&lt;0.0001)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Daily ethanol intake (g)

<table>
<thead>
<tr>
<th>Daily ethanol intake</th>
<th>Person years</th>
<th>No. of Cases (n = 101)</th>
<th>HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondrinkers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>162,184</td>
<td>32</td>
<td>1.64 (0.93–2.90)</td>
<td>1.42 (0.81–2.52)</td>
</tr>
<tr>
<td>20 – &lt;40</td>
<td>30,326</td>
<td>14</td>
<td>2.18 (1.16–4.10)</td>
<td>1.67 (0.88–3.18)</td>
</tr>
<tr>
<td>40 – &lt;80</td>
<td>25,678</td>
<td>24</td>
<td>4.39 (2.58–7.47)</td>
<td>2.88 (1.64–5.06)</td>
</tr>
<tr>
<td>80+</td>
<td>7,342</td>
<td>12</td>
<td>7.78 (3.99–15.16)</td>
<td>4.65 (2.31–9.36)</td>
</tr>
<tr>
<td>(P) for trend</td>
<td>(&lt;0.0001)</td>
<td>(&lt;0.0001)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Lifetime ethanol intake (kg)

<table>
<thead>
<tr>
<th>Lifetime ethanol intake</th>
<th>Person years</th>
<th>No. of Cases (n = 101)</th>
<th>HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondrinkers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;300</td>
<td>162,184</td>
<td>32</td>
<td>2.03 (1.24–3.31)</td>
<td>1.69 (1.03–2.77)</td>
</tr>
<tr>
<td>300 – &lt;800</td>
<td>31,437</td>
<td>20</td>
<td>2.96 (1.69–5.19)</td>
<td>2.00 (1.11–3.59)</td>
</tr>
<tr>
<td>800+</td>
<td>10,513</td>
<td>17</td>
<td>7.12 (3.92–12.94)</td>
<td>4.26 (2.26–8.01)</td>
</tr>
<tr>
<td>(P) for trend</td>
<td>(&lt;0.0001)</td>
<td>(&lt;0.0001)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(a\) Abbreviations are as follows: HR, hazard ratios; CI, confidence interval. 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.

\(b\) HRs 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).

associations between alcohol intake and esophageal cancer risk in this 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: 1) Ethanol per se is not carcinogenic; however, its major intermediary metabolite, acetaldehyde, is a recognized animal carcinogen (32); 2) alcohol may act as a solvent that enhances the penetration of carcinogens from other environmental exposures (e.g., use of tobacco and consumption of nitrosamine containing foods) (32); 3) alcohol consumption may reduce the intake and bioavailability of certain nutrients, which may have chemopreventive properties (e.g., antioxidants) (1,32); and 5) alcohol may act as a direct irritant to the esophageal epithelium that gives rise to ESCC (1).
### TABLE 4
Consumption of different types of alcoholic beverages in relation to hazard ratio of esophageal cancer, the Shanghai cohort study, 1986–2006

<table>
<thead>
<tr>
<th>Type of alcohol (Drink/Day)</th>
<th>Person years</th>
<th>No. of cases</th>
<th>HR (95% CI)(^a)</th>
<th>Adjusted HR(^b) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondrinkers</td>
<td>162,184</td>
<td>32</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Beer(^c)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>41,697</td>
<td>15</td>
<td>1.83 (0.99–3.38)</td>
<td>1.46 (0.75–2.85)</td>
</tr>
<tr>
<td>1+</td>
<td>13,403</td>
<td>7</td>
<td>2.58 (1.14–5.85)</td>
<td>1.71 (0.66–4.42)</td>
</tr>
<tr>
<td>(P) for trend</td>
<td></td>
<td></td>
<td>0.007</td>
<td>0.20</td>
</tr>
<tr>
<td>Rice wine(^d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>33,301</td>
<td>10</td>
<td>1.51 (0.74–3.07)</td>
<td>1.39 (0.66–2.90)</td>
</tr>
<tr>
<td>1 – &lt;2</td>
<td>15,261</td>
<td>12</td>
<td>3.92 (2.01–7.65)</td>
<td>3.51 (1.73–7.13)</td>
</tr>
<tr>
<td>2+</td>
<td>18,731</td>
<td>9</td>
<td>2.29 (1.09–4.81)</td>
<td>1.82 (0.82–4.01)</td>
</tr>
<tr>
<td>(P) for trend</td>
<td></td>
<td></td>
<td>0.0005</td>
<td>0.01</td>
</tr>
<tr>
<td>Spirits(^e)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>30,544</td>
<td>8</td>
<td>1.25 (0.57–2.71)</td>
<td>1.02 (0.45–2.30)</td>
</tr>
<tr>
<td>2 – &lt;4</td>
<td>16,528</td>
<td>15</td>
<td>4.28 (2.31–7.94)</td>
<td>2.87 (1.48–5.58)</td>
</tr>
<tr>
<td>4+</td>
<td>10,451</td>
<td>18</td>
<td>8.22 (4.59–14.73)</td>
<td>4.93 (2.60–9.36)</td>
</tr>
<tr>
<td>(P) for trend</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

\(^a\)Abbreviations are as follows: HR, hazard ratio; CI, confidence interval. 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.

\(^b\)HRs 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).

\(^c\)Subjects who consumed rice wine and/or spirits only were excluded from this analysis; HRs were further adjusted for consumption of rice wine and spirits.

\(^d\)Subjects who consumed beer and/or spirits only were excluded from this analysis; HRs were further adjusted for consumption of beer and spirits.

\(^e\)Subjects who consumed beer and/or rice wine only were excluded from this analysis; HRs 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

<table>
<thead>
<tr>
<th>No. of drinks per day</th>
<th>Nondrinkers</th>
<th>&lt;4</th>
<th>4+</th>
<th>(P) for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of years of smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>13</td>
<td>9</td>
<td>2</td>
<td>0.12</td>
</tr>
<tr>
<td>Person years</td>
<td>90,151</td>
<td>30,668</td>
<td>2,540</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)(^b)</td>
<td>1.00</td>
<td>1.75 (0.75–4.11)</td>
<td>3.86 (0.86–17.26)</td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Cases</td>
<td>13</td>
<td>23</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Person years</td>
<td>60,719</td>
<td>57,932</td>
<td>12,076</td>
<td></td>
</tr>
<tr>
<td>HR(^b) (95% CI)</td>
<td>1.26 (0.58–2.73)</td>
<td>2.01 (1.00–4.01)</td>
<td>4.55 (2.03–10.18)</td>
<td></td>
</tr>
<tr>
<td>40+</td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Cases</td>
<td>6</td>
<td>13</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Person years</td>
<td>11,313</td>
<td>12,785</td>
<td>4,494</td>
<td></td>
</tr>
<tr>
<td>HR(^b) (95% CI)</td>
<td>2.18 (0.80–5.92)</td>
<td>4.13 (1.85–9.25)</td>
<td>8.00 (3.36–19.05)(^c)</td>
<td></td>
</tr>
<tr>
<td>(P) for trend</td>
<td>0.18</td>
<td>0.11</td>
<td>0.10</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Abbreviations are as follows: HR, hazard ratio; CI, confidence interval.

\(^b\)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).

\(^c\)2-sided \(P\) for interaction = 0.99.
previous study found that higher concentration (40%) of ethanol could induce severe damage to the esophageal mucosa in rabbit, whereas lower ethanol concentration (20%) had much less adverse effect (33). In our cohort in Shanghai in which 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 to 5.0 (15,35). In this study, after adjustment for alcohol intake and other potential confounders, we noted a roughly 50% increase in risk among current smokers and statistically significant associations with age at starting to smoke and number of years of smoking. Furthermore, among nonalcohol users, ever smokers exhibited a relative risk of 1.46 relative to never smokers. Therefore, although the relatively small sample size of cases in this study precludes 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).

### TABLE 6
Consumption of selected food items/groups in relation to hazard ratio of esophageal cancer, the Shanghai cohort study, 1986–2006

<table>
<thead>
<tr>
<th>Food items or groups</th>
<th>1 (Lowest)</th>
<th>2</th>
<th>3 (Highest)</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fresh Fruits</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00</td>
<td>0.53 (0.35–0.82)</td>
<td>0.29 (0.15–0.54)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Adj. HR (95% CI)</td>
<td>1.00</td>
<td>0.70 (0.45–1.09)</td>
<td>0.46 (0.25–0.88)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Orange/tangerine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00</td>
<td>0.65 (0.42–1.00)</td>
<td>0.41 (0.22–0.78)</td>
<td>0.003</td>
</tr>
<tr>
<td>Adj. HR (95% CI)</td>
<td>1.00</td>
<td>0.80 (0.52–1.23)</td>
<td>0.56 (0.30–1.05)</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Fresh vegetables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00</td>
<td>0.82 (0.29–2.32)</td>
<td>0.72 (0.26–1.98)</td>
<td>0.43</td>
</tr>
<tr>
<td>Adj. HR (95% CI)</td>
<td>1.00</td>
<td>0.83 (0.29–2.36)</td>
<td>0.71 (0.26–1.95)</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>Meat</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00</td>
<td>0.99 (0.63–1.56)</td>
<td>0.77 (0.47–1.27)</td>
<td>0.31</td>
</tr>
<tr>
<td>Adj. HR (95% CI)</td>
<td>1.00</td>
<td>1.04 (0.66–1.64)</td>
<td>0.81 (0.49–1.34)</td>
<td>0.43</td>
</tr>
<tr>
<td><strong>Fish and seafood products</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00</td>
<td>1.05 (0.66–1.67)</td>
<td>0.64 (0.39–1.05)</td>
<td>0.07</td>
</tr>
<tr>
<td>Adj. HR (95% CI)</td>
<td>1.00</td>
<td>1.07 (0.67–1.70)</td>
<td>0.59 (0.36–0.97)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Egg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00</td>
<td>0.48 (0.30–0.77)</td>
<td>0.70 (0.43–1.13)</td>
<td>0.12</td>
</tr>
<tr>
<td>Adj. HR (95% CI)</td>
<td>1.00</td>
<td>0.53 (0.33–0.85)</td>
<td>0.83 (0.51–1.35)</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>Milk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00</td>
<td>0.44 (0.26–0.74)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Adj. HR (95% CI)</td>
<td>1.00</td>
<td>0.59 (0.35–1.01)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Preserved foods</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00</td>
<td>1.07 (0.66–1.73)</td>
<td>1.01 (0.62–1.63)</td>
<td>0.99</td>
</tr>
<tr>
<td>Adj. HR (95% CI)</td>
<td>1.00</td>
<td>0.99 (0.61–1.61)</td>
<td>0.94 (0.58–1.52)</td>
<td>0.79</td>
</tr>
</tbody>
</table>

*Abbreviations are as follows: HR, hazard ratio; CI, confidence interval; Adj., adjusted.*

*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.*

*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 wk 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

<table>
<thead>
<tr>
<th>Nutrients</th>
<th>1 (Lowest)</th>
<th>2</th>
<th>3 (Highest)</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00</td>
<td>0.42 (0.25, 0.70)</td>
<td>0.38 (0.22, 0.65)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Adj. HR (95% CI)</td>
<td>1.00</td>
<td>0.58 (0.35, 0.97)</td>
<td>0.72 (0.41, 1.26)</td>
<td>0.20</td>
</tr>
<tr>
<td>Fat</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00</td>
<td>1.05 (0.62, 1.77)</td>
<td>0.62 (0.32, 1.19)</td>
<td>0.08</td>
</tr>
<tr>
<td>Adj. HR (95% CI)</td>
<td>1.00</td>
<td>1.40 (0.83, 2.36)</td>
<td>1.21 (0.63, 2.31)</td>
<td>0.55</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00</td>
<td>0.58 (0.36, 0.94)</td>
<td>0.51 (0.31, 0.83)</td>
<td>0.01</td>
</tr>
<tr>
<td>Adj. HR (95% CI)</td>
<td>1.00</td>
<td>0.76 (0.47, 1.24)</td>
<td>0.90 (0.53, 1.51)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

*Abbreviations are as follows: HR, hazard ratio; CI, confidence interval; Adj., adjusted.

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.

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.

Results of this 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 that have been conducted in Chinese populations (13,37). Some reduction in esophageal cancer risk was associated with increased consumption of milk (the major dairy 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, whereas smokers are known to have low intake and circulating levels of antioxidants including carotenoids and vitamin C than nonsmokers (42,43).

Despite these limitations, this study has several strengths. The strengths include the population-based study design, long duration of follow-up (up to 20 yr), 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.

ACKNOWLEDGMENTS

We thank Ms. Xue-Li Wang, Ms. Yue-Lan Zhang, and Ms. Jia-Rong Cheng of the Shanghai Cancer Institute for their assistance in data collection and management and the staff of the Shanghai Cancer Registry for their assistance in verifying cancer diagnoses in study subjects. This work was supported...
by the United States National Institutes of Health (Grant R01 CA43092).

REFERENCES
