

1 **Hot tea consumption and its interactions with alcohol consumption**
2 **and tobacco smoking on risk of esophageal cancer: a population-**
3 **based cohort study**

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Abstract

Background: While the high-temperature tea consumption has been suggested as a risk factor for esophageal cancer (EC), this has not been consistently observed and whether it is independent of alcohol and tobacco exposure has not been evaluated.

Objective: To examine the joint association of high-temperature tea consumption and established risk factors of alcohol consumption and smoking on EC risk.

Design: China Kadoorie Biobank, prospective cohort study established during 2004-08.

Setting: Ten areas across China.

Participants: 456,155 participants aged 30-79 years after excluding participants with cancer at baseline and those who had cut down consumption of tea, alcohol, or tobacco before baseline.

Measurements: The usual temperature at which tea was consumed, other tea consumption metrics, and lifestyle behaviors were self-reported once at baseline. Outcome was EC incidence until 2015.

Results: During a median of 9.2 years of follow-up, we documented 1,731 incident EC cases. We found that high-temperature tea consumption in combination with either alcohol consumption or smoking had a greater risk of developing EC than high-temperature tea consumption alone. Compared with participants who consumed tea less than weekly and consumed alcohol <15g per day, those daily consumers who preferred burning hot tea and consumed alcohol ≥ 15 g had the greatest risk of developing EC (hazard ratio=5.00; 95% CI: 3.64, 6.88). Similarly, the hazard ratio (95% CI) for those who were both current smoker and

56 daily tea consumer preferring burning hot tea was 2.03 (1.55, 2.67).

57 **Limitations:** Tea consumption was self-reported once at baseline, leading to the possibility of
58 nondifferential misclassification and attenuation of the association.

59 **Conclusion:** Our findings highlight the importance of abstaining from high-temperature tea in
60 excessive alcohol consumers and smokers on EC prevention.

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Introduction

Esophageal cancer (EC) remains a global concern because of its increasing incidence and persistently poor survival.(1, 2) It poses a bigger threat to less developed regions and men. Both alcohol consumption and tobacco smoking are well-established causes of esophageal squamous cell cancer (ESCC),(3) the most common histological subtype globally.(2) Limited evidence suggests decreased risk of ESCC with higher consumption of vegetables and fruits and increased physical activity, and increased risk with higher consumption of processed meat.(3)

Tea is one of the most common beverages worldwide and usually consumed at elevated temperature. Existing evidence remains inconclusive as to the association between tea consumption and EC risk. Numerous experimental studies have demonstrated inhibitory effects of tea against tumorigenesis in the digestive tract.(4) On the other hand, chronic thermal injury to the esophageal mucosa may initiate carcinogenesis. Drinking scalding (>65°C) beverages have recently been classified as probably carcinogenic to humans by the International Agency for Research on Cancer (IARC).(3, 5) A few epidemiological studies have addressed the association of EC with tea consumption regarding frequency, amount consumed, or tea temperature, but the results were substantially conflicting.(6-12) Except for few prospective studies with limited incident cases,(13-16) the vast majority of studies followed case-control design, which is particularly vulnerable to several biases, including recall bias and reverse causality due to change of drinking habits by prediagnostic EC cases following their symptoms.

China is among the countries with the highest EC incidence. Tea consumers, especially in Chinese men, are more likely to smoke and drink alcohol. Tobacco smoking and alcohol consumption, as well as the chemical compounds and adverse thermal effect of high-temperature tea, considerably complicate the association between tea consumption and EC risk. In the China Kadoorie Biobank (CKB) study of 0.5 million adults, we prospectively examined the joint association of tea consumption metrics, especially tea temperature, and established risk factors of smoking and alcohol consumption on EC risk.

Methods

Study population

The CKB cohort was established in ten study areas geographically spread across China, including five urban areas and five rural areas. During 2004-2008, 512,891 adults aged 30-79 years were enrolled with valid baseline data, including completed questionnaire, physical measurements, and a written informed consent form. Trained staff entered baseline information directly into a laptop-based data entry system developed with built-in functions to avoid missing items and minimize logic errors during the interview. Further detailed description is available elsewhere.(17, 18) The Ethical Review Committee of the Chinese Center for Disease Control and Prevention (Beijing, China) and the Oxford Tropical Research Ethics Committee, University of Oxford (UK) approved the study.

For the present analysis, we excluded participants with previously diagnosed cancer ($n=2,577$), and those who had missing data for body mass index ($n=2$) or were lost to follow-

up shortly after baseline ($n=1$). To avoid potential reverse causality, we further excluded participants whose consumption frequency of tea ($n=11,578$) or alcohol ($n=20,952$) had reduced from at least weekly to less than weekly, and former smokers ($n=30,563$) who had stopped smoking for ≥ 6 months. The final analysis included 456,155 participants.

Assessment of tea consumption

In the baseline questionnaire, we asked participants to report their usual frequency of tea consumption (never, only occasionally, only at certain seasons, monthly but less than weekly, or at least once a week) during the past 12 months. Participants who consumed tea less than weekly were asked whether they ever had consumed tea weekly for at least one year. Participants who consumed tea weekly were asked about their days consumed in a typical week (1-2, 3-5, or 6-7 days), cups of tea (in 300 ml-sized cup) in one drinking day, tea leaves (in gram) added each time, times of changing tea leaves in one drinking day, type of tea consumed most commonly (green tea, oolong tea, black tea, or others), usual temperature at which tea was consumed (room temperature/warm, hot, or burning hot), and age since they started drinking tea weekly. We provided a pictorial guide for participants that explained what a standard-sized cup and different grams of tea leaves look. The tea leaves added in one drinking day was calculated by multiplying tea leaves (in gram) added each time by times of changing tea leaves. Among 4,405 weekly tea consumers who completed the same questionnaire twice at an average interval of 2.6 years between baseline survey and a subsequent re-survey,⁽¹⁷⁾ spearman's correlation coefficient was 0.35 for tea temperature

preference, 0.53 for cups of tea consumed, and 0.63 for tea leaves added.

Assessment of tobacco smoking, alcohol consumption, and other covariates

We asked ever smokers to report their frequency, type, and the amount of tobacco (in cigarette or equivalent amount of tobacco; 1 cigarette = 1 gram of tobacco = 0.5 cigars (19)) smoked per day, and time since quitting for former smokers. Participants who reported having stopped smoking for less than six months were still regarded as current smokers and included in the present analysis. We asked participants who drank alcohol at least once a week in the past 12 months about their typical consumption frequency, type of alcoholic beverage consumed habitually, and the amount of alcohol consumed on a typical drinking day. Based on this information, we calculated pure alcohol intake in grams on a typical drinking day.(20) We also asked less-than-weekly consumers whether they ever had an experience of consuming alcohol weekly for at least one year.

Other covariates inquired in the baseline questionnaire included socio-demographic characteristics (age, sex, education, marital status, and household income), lifestyle behaviors (physical activity, and intakes of red meat, fresh fruits and vegetables, and preserved vegetables), women's menopausal status, and family history of cancer. Trained staff measured weight and height using calibrated instruments.

Ascertainment of EC cases

We ascertained incident EC cases since the participants' enrollment into the study at baseline

by linking to local disease and death registries, to the national health insurance system, and by active follow-up.(17) Trained staff, blinded to the baseline information, coded all cases using the 10th revision of the International Classification of Diseases. For the present analysis, EC cases were defined by code C15. In the CKB study, ongoing retrieve of medical records of incident cases is in process. Trained staff review medical records for diagnosis validation and further collection of detailed clinical information such as pathology subtype. Up to now, we have retrieved medical records for 870 newly reported EC cases during follow-up, among which 843 (96.9%) were confirmed as EC cases, and 65.4% (569/843 cases) had pathology reports. After excluding 37 cases with subtype reported as “unknown”, 91.9% (489/532 cases) were esophageal squamous cell cancer.

Statistical analysis

We calculated person-years at risk from the baseline date to the diagnosis of EC, death, loss to follow-up, or December 31, 2015, whichever came first. The loss to follow-up in the CKB study refers to a participant whose permanent registered residence has moved out of the jurisdiction of the Regional Coordinating Center. By December 31, 2015, of all 512,891 participants, 37,289 (7.3%) died and 4,875 (<1%) were lost to follow-up. We used Cox proportional hazards model to estimate the hazard ratio (HR) and 95% confidence interval (CI), with age as the underlying time scale and stratified jointly by ten study areas and age at baseline in 5-year interval. Test and graph based on Schoenfeld residuals showed that the proportional hazards assumption was satisfied.

Multivariable models were adjusted for age, sex, education, marital status, household income, tobacco smoking, alcohol consumption, physical activity, intakes of red meat, fresh fruits and vegetables, and preserved vegetables, body mass index, family history of cancer, and menopausal status (for women only). Forty women had missing data for menopausal status. We included an indicator for the missing data category. There are no missing data for other variables. We tested linear trend of EC risk across different metrics of tea consumption by modeling the levels of ordered categorical variable as a continuous variable in a separate model.

We examined whether the association between tea temperature preference and EC risk differed by tobacco smoking or alcohol consumption. We tested multiplicative interaction by using likelihood ratio test comparing models with and without cross-product term. We also plotted the covariate-adjusted cumulative incidences of EC based on Cox for participants with different consumption combinations of tea temperature, tobacco, and alcohol separately, accounting for death as a competing risk. Specifically, after fitting the competing-risks regression model (*stcrreg* procedure), we used *stcurve* procedure to plot.(21)

We performed all statistical analyses using Stata (version 14.2, StataCorp).

Role of the Funding Source

The funders had no role in the study design, data collection, data analysis and interpretation, writing of the report, or the decision to submit the article for publication.

Results

Participants in the present analysis had a mean age of 50.9 ± 10.5 years. Of 456,155 participants, 42.1% of men and 16.1% of women consumed tea daily. Both male and female participants who reported preferring burning hot tea were more likely to be current smokers, drank alcohol daily, drank more cups of tea and added more tea leaves per day (Appendix Table 1).

Tea temperature preference, other metrics of tea consumption, and EC

During a median of 9.2 years (4.1 million person-years) of follow-up, we documented 1,106 incident EC cases in men and 625 in women. In the multivariable-adjusted model of the male participants, daily tea consumption was associated with increased EC risk, with higher risk seen in participants who reported preferring hotter tea (Table 1). The association exhibited a clear attenuation after further adjustment for tobacco smoking and alcohol consumption. Compared with men consuming tea less than weekly, the HRs (95% CIs) for EC were 1.17 (0.91, 1.50), 1.30 (1.05, 1.59), and 1.55 (1.19, 2.02) for those daily consumers whose preferred tea temperature was warm, hot, and burning hot, respectively. There was no statistically significant association between tea temperature and EC in women ($P < 0.001$ for interaction with sex).

We also observed statistically significant increased risk of EC with more cups of tea consumed, more tea leaves added, longer duration of tea consumption, and green tea in men (Appendix Tables 2, 3, 4, and 5; all P for interaction with sex < 0.001). The information on various metrics of tea consumption was only available among regular tea consumers, we,

therefore, further adjusted for tea temperature preference and other metrics of tea consumption mutually among male daily tea consumers. Men preferring burning hot tea showed a higher risk of EC than those preferring hot and warm tea, but the association did not reach statistical significance (Appendix Table 6). No association was observed for other consumption metrics.

Tea temperature preference with alcohol consumption or smoking on EC

We observed important differences in the association between tea temperature preference and EC risk across stratum for alcohol consumption (Table 2, $P < 0.001$ for interaction) or tobacco smoking (Table 3, $P = 0.001$ for interaction), with a stronger association in participants who consumed alcohol ≥ 15 g per day or in current smokers. Compared with participants who consumed tea less than weekly and consumed alcohol < 15 g per day, those daily consumers who preferred burning hot tea and consumed alcohol ≥ 15 g had the greatest risk of developing EC (HR=5.00; 95% CI: 3.64, 6.88). Similarly, the HR (95% CI) for those who were both current smoker and daily tea consumer preferring burning hot tea was 2.03 (1.55, 2.67).

Joint association of tea temperature preference, alcohol consumption, and smoking on EC

We further examined the joint association of the three factors on EC risk. Figure 1 shows the adjusted cumulative incidences of EC by combined categories of tea temperature, tobacco and alcohol consumption. In the absence of smoking and excessive alcohol consumption, daily tea consumption was not associated with increased EC risk, at whatever tea temperature (Table 4) or in whatever other consumption metrics (Appendix Table 7). The EC risk increased for daily

tea consumers who preferred hot or burning hot tea in the presence of either smoking (HR=1.56; 95% CI: 1.21, 2.02) or excessive alcohol consumption (HR=2.27; 95% CI: 1.16, 4.45). The strongest association was seen in the combination of daily high-temperature tea consumption with both smoking and excessive alcohol consumption (HR=5.01; 95% CI: 4.00, 6.28). Other metrics of tea consumption showed less clear patterns of joint association with smoking and excessive alcohol consumption.

Sensitivity analysis (data not shown)

The association of tea temperature preference with EC risk persisted after excluding cases who were diagnosed during the first two ($n=339$) or four ($n=706$) years of follow-up. The results also did not change appreciably when we tried more comprehensive adjustments for tobacco smoking by using pack-years, and for alcohol consumption by additionally including years of alcohol consumption. When we used competing-risks regression to take into account the competing risk of death, the subhazard ratios obtained in the competing-risks regression were not altered much compared with HRs obtained in the Cox regression.

Discussion

In this large prospective Chinese cohort, we found that the association between high-temperature tea consumption and EC risk was dependent on alcohol and tobacco consumption. There was synergistic associations of high-temperature tea consumption with excessive alcohol consumption or smoking on EC risk. Those who had clustering habits of consuming high-temperature tea, excessive alcohol, and tobacco had a risk of developing EC

over five times as high as those who consumed none. However, in the absence of both excessive alcohol consumption and smoking, daily tea consumption was not associated with EC risk, at whatever tea temperature or in whatever other consumption metrics.

Comparison with other studies and potential mechanism

Only a few prospective studies have examined the association of EC risk with tea temperature (13) or amount of tea consumed (14-16) and shown inconsistent findings. Several systematic reviews and meta-analyses of principally case-control studies suggested no clear pattern of association between the amount of tea consumed and EC risk, but increased EC risk associated with higher-temperature tea consumption.(6-12) Previous studies also indicated that hot food and beverage consumption was associated with the risk of ESCC but not esophageal adenocarcinoma.(12, 22) In the present Chinese population, in which ESCC is the predominant histological subtype, we observed that high-temperature tea consumption, was prospectively associated with EC risk in the presence of excessive alcohol consumption or smoking; but there was no such association in the absence of both habits.

The synergistic associations of high-temperature tea, excessive alcohol, and tobacco on EC risk are biologically plausible. It is suggested that thermal injury may result in epithelial damage and impaired barrier function, subsequently augment the risk of damage from other risk factors, such as excessive alcohol consumption and smoking.(22) The release of *N*-nitroso compounds (NOCs), which are formed as a result of inflammatory processes associated with chronic thermal irritation of the esophageal mucosa, may also contribute to the development of EC.(22, 23) The mechanism for their joint associations on EC still

warrants further elucidation.

Different metrics of tea consumption were interrelated in the present population. It increased the difficulty in identifying what was the most relevant metric in relation to EC risk. In the present study, there was evidence of increased EC risk with preferred tea temperature. For other metrics of tea consumption, increased EC risk was also observed such as among those who consumed more cups of tea or added more tea leaves. However, we considered the hypothesis that higher tea temperature was associated with increased EC risk to be more biologically plausible. Additional studies are needed to confirm our findings.

In contrast to the strong and relatively consistent evidence for the potential anticarcinogenic properties of tea bioactive compounds from experimental studies,(4) results from epidemiological studies have not convincingly shown the EC preventive effect of tea consumption in humans.(6-12) The majority of the inverse association between tea consumption and EC risk was found in case-control studies of East-Asian countries, especially China. It was supposed that the protective effects of tea consumption, if any, on EC development could be overshadowed by alcohol consumption and smoking, as well as the thermal effect of high-temperature tea.(24) However, in the present population, when we restricted analyses to the subgroup of participants who were both non-heavy alcohol consumers and non-smokers, daily tea consumption in whatever consumption metrics or type of tea was not associated decreased EC risk. In an early randomized controlled trial of 200 participants from Henan of China, decaffeinated green tea did not show beneficial effects in alleviating precancerous lesions and abnormal cell proliferation patterns after 11 years of

follow-up.(25) A nested case-control study from Shanghai men cohort also did not find association between urinary tea polyphenol biomarkers and EC risk.(26) The difference between the results from animal studies and human studies with high level of evidence quality is likely to be due to the relatively low human exposure to tea polyphenols, in the range of 1 to 2 orders lower than those used in animal studies.(4)

Strengths and limitations of this study

To the best of our knowledge, the present study, for the first time, provides compelling evidence of joint associations of high-temperature tea with established risk factors of excessive alcohol and tobacco on EC risk. Strengths of the study include prospective design, the inclusion of a geographically spread Chinese population living in urban and rural areas, and careful adjustment for potential confounders. To avoid potential reverse causality bias, we particularly excluded participants who had cut down on tea, alcohol, or tobacco, and further excluded EC cases who were diagnosed during the first several years of follow-up. The CKB study collected detailed information on several metrics of tea consumption, including frequency, amount, duration, type of tea, and qualitative gradation of tea temperature, so that we could analyze comprehensively and mutually adjust for each other.

Some limitations also warrant mention. Tea consumption patterns were self-reported and collected once at baseline. The consumption habits may change over time. Nevertheless, exposure misclassification might be nondifferential on subsequent disease status and have attenuated our findings. The tea temperature relied on qualitative self-report data and was not validated with actual temperature measurement. We did not ask sip size, which, together with

the initial tea temperature, determine the intraesophageal temperature (27) and lead to differences in subjective perception of temperature. To obtain a valid and reliable estimate of the temperature at which participants typically drink tea is a challenge for most of the epidemiological studies. The present study lacked information on histological subtype of each EC cases. However, ESCC accounts for >90% of EC cases in a subset of cases of the present population and also in China.(28) The preference of hot tea may be correlated with other consumption habits of hot beverages and foods, which we did not collect and adjust for in our analyses. Thus the thermal injury from other hot beverages and foods may also contribute to the observed associations. Despite the overall large sample size, few women consumed tobacco and alcohol in the present population, leading to wide CIs for the effect estimates and inconclusive results in women, and precluding the further sex-specific joint analysis of relevant factors. Also, when we further examined three-way association, such as among tea temperature, alcohol consumption, and tobacco smoking, or among tea temperature, frequency of tea consumption per day, and alcohol consumption (or tobacco smoking), cases were too small to get reliable effect estimates for three categories of tea temperature.

Conclusion

Our findings showed a noticeable increase in EC risk associated with a combination of consuming high-temperature tea, excessive alcohol, and tobacco. It highlights the importance of abstaining from high-temperature tea in excessive alcohol consumers and smokers on EC prevention. More prospective studies are warranted to confirm the interactions observed in this study. Studies in which the actual tea temperature is measured are particularly

encouraged.

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Contributors: JL and LL conceived and designed the paper. LL, ZC, and JC, as the members of CKB steering committee, designed and supervised the conduct of the whole study, obtained funding, and together with YG, ZB, LY, YC, AT, and XZ coordinated the data acquisition (for baseline, resurveys, and long-term follow-up) and standardization. CY, JL, HT, and XY analyzed the data. CY and JL drafted the manuscript. JL and LL contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content. All authors contributed to and approved the final manuscript. JL and LL are the study guarantors.

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Figure legends

Figure 1. Adjusted cumulative incidences of EC for participants with different consumption combinations of tea, alcohol, and tobacco

(A) Nonsmoking, and less than daily or <15 g/day alcohol consumption; (B) Current smoking, and less than daily or <15 g/day alcohol consumption; (C) Nonsmoking, and ≥ 15 g/day alcohol consumption; (C) Current smoking, and ≥ 15 g/day alcohol consumption. The reference group was participants who consumed tea less than daily and alcohol less than daily or <15g per day, and were nonsmoker. The multivariable model was adjusted for age, sex, study areas, education, marital status, household income, physical activity, intakes of red meat, fresh fruits and vegetables, and preserved vegetables, body mass index, and family history of cancer.