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A prospective study of tea drinking temperature and risk of esophageal squamous cell carcinoma

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Abstract

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Previous studies have reported an association between hot tea drinking and risk of esophageal cancer, but no study has examined this association using prospectively and objectively measured tea drinking temperature. We examined the association of tea drinking temperature, measured both objectively and subjectively at study baseline, with future risk of esophageal squamous cell carcinoma (ESCC) in a prospective study. We measured tea drinking temperature using validated methods and collected data on several other tea drinking habits and potential confounders of interest at baseline in the Golestan Cohort Study, a population-based prospective study of 50,045 individuals aged 40–75 years, established in 2004–2008 in northeastern Iran. Study participants were followed-up for a median duration of 10.1 years (505,865 person-years). During 2004–2017, 317 new cases of ESCC were identified. The objectively measured tea temperature (HR 1.41, 95% CI 1.10–1.81; for ≥60°C vs. <60°C), reported preference for very hot tea drinking (HR 2.41, 95% CI 1.27–4.56; for "very hot" vs. "cold/lukewarm"), and reported shorter time from pouring tea to drinking (HR 1.51, 95% CI 1.01–2.26; for <2 vs. ≥6 minutes) were all associated with ESCC risk. In analysis of the combined effects of measured temperature and amount, compared to those who drank less than 700 ml of tea/day at <60°C, drinking 700 ml/day or more at a higher-temperature (≥60°C) was consistently associated with an about 90% increase in ESCC risk. Our results substantially strengthen the existing evidence supporting an association between hot beverage drinking and ESCC.

Keywords

esophageal cancer; hot beverages; Iran; risk factor

Introduction

Multiple observational studies have reported an association between hot beverages and esophageal cancer.[1–3] However, except for three prospective studies,[4–6] previous studies on this association have been of retrospective design, which may be prone to recall bias.[1–3] A major limitation of all previous prospective studies is that tea drinking temperature data have been based on self-reported perception of tea drinking temperature, which may vary across individuals and populations and could not be objectively verified. Due to these limitations, the International Agency for Research on Cancer (IARC) has concluded that the existing evidence in humans for the carcinogenicity of drinking hot beverages is limited and has classified "drinking very hot beverages at above 65°C" as "probably carcinogenic" (Group 2A according to IARC's classification system of carcinogens), rather than "carcinogenic" to humans (Group 1).[1, 7]

Very high incidence rates of esophageal cancer have been reported from the Golestan Province, northeast of Iran,[8] where esophageal squamous cell carcinoma (ESCC) constitutes more than 90% of esophageal cancers.[9] Two previous case-control studies from the Golestan Province reported an association between hot tea drinking and esophageal cancer.[10, 11] Both of these studies were limited by their retrospective design and using only self-perceived reporting of tea drinking temperature. In 2004, we initiated the Golestan Cohort Study, a large prospective study of over 50,000 in the same region.[8, 12] To our knowledge, this is the only large-scale prospective study in the world in which actual tea drinking temperature has

been measured by trained staff at baseline.[13] Herein, we examine the association of prospectively measured tea drinking temperature, as well as subjective preference for hot tea drinking, time from pouring tea to drinking, and other tea drinking habits with ESCC risk using data from the Golestan Cohort Study.

Methods

Study population.

The design of the Golestan Cohort Study has been described elsewhere,[13] and a more detailed summary of the study methods is available in Supplementary Methods. Briefly, it is a prospective population-based cohort of 50,045 individuals, 40–75 years old, which was established between January 2004 and June 2008 in the eastern part of Golestan Province.

Written consent was obtained from all participants. The conduct of Golestan Cohort Study was approved by the institutional review boards of the Digestive Disease Research Institute of Tehran University of Medical Sciences, the U.S. National Cancer Institute, and the International Agency for Research on Cancer.

Exposure assessment.

Trained staff collected information on a wide range of personal characteristics and potential risk factors of ESCC using a structured questionnaire in face to face interviews. A composite score for wealth was calculated by applying multiple correspondence analysis to appliance ownership data, including personal car, motorbike, black and white TV, color TV, refrigerator, freezer, vacuum cleaner, and washing machine.[14] Average fresh fruit and vegetable intake per day was calculated using data collected through a food frequency questionnaire specifically designed for this population.[15] Cigarette smoking was classified as never, former (those who quit more than 1 year before enrolment), or current smokers at baseline. Nass (a chewing tobacco product), opium, and alcohol use were classified as never and ever users.

Tea and water are the only drinks commonly consumed in Golestan, of which only tea is generally consumed at a high temperature.[11, 16] We asked those who drank tea about the interval (in minutes, ranged from 0 to ≥10 minutes) between tea being poured and drunk and whether they usually drank tea warm/lukewarm, hot, or very hot. Further, we measured the temperature of tea drunk by the participants using a method that had shown good reliability in the pilot phase of the cohort study.[17] We prepared two fresh cups of tea at the time of interview for each participant, one for the participant and the other for the interviewer to measure the temperature using a digital thermometer. When the tea temperature was 75°C, participants were asked to sip the tea. If it was their usual tea drinking temperature or they usually drank higher temperature tea, it was recorded. Otherwise, the procedure was repeated by allowing the tea to cool to 70°C, or if necessary, to lower temperatures (at 5°C intervals). The lowest temperature category was 60°C. The tea temperature for the participants who drank tea at colder temperatures was recorded as <60°C.

In addition, trained nutritionists collected information on the amount of black and green tea consumed using the study food frequency questionnaire, which included questions about the

volume of the usual cups used for and frequency of tea drinking.[15] To increase the accuracy of the reported volume, photographs of five types of cups and mugs commonly used in Golestan were provided.

Case ascertainment.

All study participants are annually followed up through active telephone surveys and home visits by our staff. Further, monthly provincial death registration data and local health workers' reports are reviewed to identify additional cancer cases and deaths. Losses to follow-up in the Golestan Cohort Study has been less than 1%. The end of follow-up for the present study was the date of first diagnosis of esophageal cancer for cancer cases, the date of death for deaths from any other causes, and the date of last follow-up for other participants, through December 31, 2017. The median duration of follow-up was 10.14 years (505,865 person-years), during which 328 primary esophageal cancers cases identified based on history, imaging, and/or other medical reports. The histological report was available for 296 cases (90.2%), among whom squamous cell carcinoma was the predominant subtype (285 cases, 96.3%); the remaining 11 cases had esophageal adenocarcinoma. The latter 11 cases were excluded from this analysis, leaving 317 histologically confirmed ($N = 285$) or likely ($N = 32$) ESCC cases.

Statistical analysis.

After excluding 7 participants with upper gastrointestinal cancer at the time of recruitment and 11 cases of esophageal adenocarcinoma identified during follow-up, 50,027 participants were included in this analysis. Black tea consumption is very common in the area, and the average amount of black tea consumed in milliliters per day was categorized in 5 categories by quintiles (rounded to the nearest 100 ml/day) based on baseline data. As most participants did not drink green tea, those who did were categorized in two groups of nearly equal size based on baseline data (average consumption of 1–39 and ≥40 ml/day). The measured tea temperature was categorized as <60, 60–64, and ≥65°C, as the recorded tea temperature of 60°C indeed represented temperatures from 60°C to less than 65°C, and we combined 65°C and higher temperatures due to small numbers. Participants with one or more missing values in tea drinking variables (<3% of the cohort for any tea variable) were excluded from corresponding analyses. Those who did not drink tea were excluded from tea temperature analyses.

Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for the association between tea drinking habits and ESCC risk. As distributions of established risk factors or factors with previously reported associations with ESCC in Golestan were different by tea variables, we adjusted HRs for those factors, as shown in Table 1.[14, 18] We also provide HRs for tea temperature variables after being additionally adjusted for black tea and green tea consumption, and HRs for black and green tea consumption after being additionally adjusted for measured tea temperature and consumption of the other tea type. Further, we examined combined associations of measured tea temperature and total tea (black plus green) consumption with ESCC risk.

We repeated the latter analysis among never and ever cigarette and/or alcohol users, as a large-scale prospective study in China recently reported a positive association between hot tea drinking and esophageal cancer only among those with tobacco or excessive alcohol use.[6] Other additional analyses were conducted by sex, for those with histologically confirmed ESCC, and after excluding ESCC cases occurred in the first 2 years of follow-up, to allow for possible changes in drinking habits due to early symptoms of the disease or pre-neoplastic lesions. Based on Schoenfeld residuals,[19] the proportional hazards assumption was not violated in any Cox proportional hazards regression models in this study; global test *P* values ranged from 0.17 to 0.99 for main analyses and from 0.10 to 0.83 for additional analyses. We used likelihood ratio tests comparing fully adjusted Cox models with and without interaction terms to examine interactions between tea temperature (<60°C, ≥60°C) and amount (1–699 ml/day, ≥700 ml/day) for ESCC risk among tea drinkers. All statistical analyses were performed using Stata statistical software version 13 (Stata Corporation, College Station, Texas, USA).

Results

The average daily consumption of black and green tea in the entire cohort was 1,174 and 42 ml/day, respectively (Appendix Table 1). Older people, men, rural dwellers, non-Turkmens, people with lower education or wealth score, cigarette smokers (former or current), and nass, opium, and alcohol users drank tea at higher temperatures (Table 1). Those who drank greater amounts of black tea were also more likely to drink tea at ≥65°C (Appendix Table 2).

All tea temperature variables considered in this analysis were associated with ESCC risk (Table 2). In fully adjusted models, the HR (95% CI) for drinking tea at ≥60°C, compared to <60°C, was 1.41 (1.10–1.81); the HRs for drinking tea at 60–64°C and ≥65°C were comparable. Drinking self-perceived very hot tea was also associated with ESCC risk (HR 2.41, 95% CI 1.27–4.56), compared to cold or lukewarm tea. Consistent with this finding, shorter duration from pouring to drinking was associated with higher risk (HR 1.10, 95% CI 1.01–1.21 per 2-minute shorter intervals vs. ≥10 minutes), although only self-reported durations of less than 5 minute appeared to be associated with the increased risk. Higher consumptions of black tea, green tea, and black and green tea combined were also associated with ESCC risk (Table 2).

Combination of tea temperature and amount.

Compared to drinking 1–699 ml/day tea (black and green combined) at <60°C, HRs (95% CI) for drinking tea at the same low temperature was 0.95 (0.52–1.74) for 700–1299 ml/day and 1.66 (0.95–2.89) for ≥1300 ml/day (Table 3). However, only a relatively small number of ESCC cases drank tea at <60°C. Compared to the same reference group, drinking 1–699 ml/day tea at ≥60°C did not show an association with ESCC risk (HR 1.10, 95% CI 0.61–2.00), but drinking 700–1299 ml/day (HR 1.95, 95% CI 1.17–3.25) and ≥1300 ml/day (HR 1.87, 95% CI 1.13–3.11) tea at ≥60°C did. However, we did not find a statistically significant interaction between tea temperature and amount for ESCC risk ($P = 0.39$).

The HRs were generally similar in additional subgroup analyses by sex or history of cigarette and alcohol use, for histologically confirmed ESCC cases, or after excluding ESCC

cases occurred in the first 2 years of follow-up, although 95% CIs became slightly wider due to smaller numbers of events (Appendix Table 3). A noticeable difference was an increased risk associated with drinking ≥1300 ml/day tea at <60°C among ever cigarette or alcohol users, among whom HRs for drinking tea at ≥60°C were also slightly greater than in other subgroups. However, this group included only 70 ESCC cases (with 5 cases in the reference group) and a much smaller number of non-cancer participants due to the relatively low prevalence of these habits in this population.

Discussion

In this study, the measured tea temperature, reported preference for very hot tea drinking, and reported shorter time from pouring tea to drinking were each associated with ESCC risk. In analysis of the combined effects of measured temperature and amount, drinking 700 ml/day tea or more at ≥60°C was associated with about 90% higher risk of ESCC. Since in this study cigarette smoking prevalence was relatively low (particularly in women) and alcohol consumption was negligible,[20] there would be minimal residual confounding from smoking and alcohol, which could be a problem in other studies.

Only two prospective cohort studies have previously examined the association between hot tea drinking and esophageal cancer. In a study in Japan, consumption of hot tea (vs. non-hot) was associated with a 1.5-fold increased risk of esophageal cancer death.[5] The other prospective study showed an adverse association only among tobacco and excessive alcohol users in China; compared to non-heavy drinkers (defined as drinking <15 g/day of alcohol) and non-smokers who drank tea less than daily, the relative risk (RR) for drinking hot/burning hot tea in a daily basis was 1.6 for non-heavy alcohol drinking smokers, 2.3 for non-smoking heavy drinkers, and 5.0 for heavy drinking smokers,[6] although there is the possibility that the latter higher RRs (with drinking ≥15 g/day alcohol) resulted partly from a residual confounding effect of alcohol. However, the lack of an association among non-tobacco or alcohol users in that study is likely related to relatively small sample size of that group; for example, the total number of non-smoker cancer cases who daily drank tea was 75, compared to 360 cases among smokers.[6] A third prospective study examined the association between unspecified hot liquid consumption and esophageal cancer but showed no association (RR, 0.96).[4] However, that study asked only two very general questions ("How often do you drink hot liquids in the" "summer" and "winter?") and the analysis compared only two categories (≥1 vs. 0 time per year).[4]

Multiple case-control studies have also shown an association between hot beverages, including tea, maté, and coffee, and esophageal cancer risk.[3] When results are available by histological subtype, positive associations have been reported for ESCC.[3] However, evidence on esophageal adenocarcinoma is limited to a handful of small-scale case-control studies in Western populations, where beverages are usually consumed at more moderate amounts and temperatures.[3] Earlier studies of hot beverages and esophageal cancer generally do not provide data on actual tea drinking temperature, but some more recent case-control studies have examined the association by measuring tea temperature in cases after the development of cancer and in controls.[21, 22] However, this measurement does not consider any changes in temperature preferences or in dietary habits in cancer cases that could happen

due to the disease. Previous case-control studies from Golestan reported a stronger association between drinking very hot tea and ESCC risk based on self-perceived data[10, 11] than the current study. This could be in part related to some recall bias, as well as a decrease in temperature preferences or the amount of hot tea consumed in the region over time because of changes in dietary habits and availability of safe water.[16] Further, drinking tea temperature preference among some participants in this study could have decreased over the 10-year follow-up period, perhaps after publication of our previous report in 2009;[11] we did not update tea temperature data during the follow-up. However, even with a relatively moderate magnitude of association, hot tea drinking is likely to be an important contributor to the high incidence of ESCC in Golestan due to its high prevalence and high quantities in both sexes.

Several mechanisms might explain how drinking hot beverages could lead to ESCC. Thermal injury may increase ESCC risk by inducing inflammatory processes, which might directly affect DNA bases and/or increase the formation of carcinogenic *N*-nitroso compounds.[23, 24] Another likely mechanism is an impairment in the barrier function of the esophageal mucosa because of thermal injury, perhaps after reaching a threshold temperature,[25] which might increase exposure to intraluminal carcinogens, including *N*-nitroso compounds and polycyclic aromatic hydrocarbons (PAHs). A few animal studies have examined the association between administration of hot water with or without *N*-nitroso compounds and esophageal neoplasia. In those studies, hot water by itself did not show positive results, but it increased the incidence of esophageal pre-neoplastic or neoplastic lesions induced by *N*-nitroso compounds.[26–29] In two studies that examined this effect at two different temperatures, administration of water at 65–70°C, but not at 55–60°C, was associated with the increase.[28, 29]

The status of exposure to *N*-nitroso compounds in Golestan is unknown, but a very high exposure to PAHs has been reported in this population.[30, 31] Current evidence suggests an association between PAHs and ESCC, although a causal association is yet to be established.[32] PAHs are products of incomplete combustion of organic matter, and exposure to PAHs is common in smokers.[33] In Golestan, however, even non-smokers are also highly exposed to PAHs, most probably through diet.[18, 34] A study comparing samples of non-tumoral esophageal epithelium from ESCC cases and controls in Golestan showed substantially higher levels of a PAH biomarker in cases.[35] However, another study has suggested that drinking very hot beverages per se may be causally associated with esophageal cancer risk, with minimal contribution from exposure to PAHs.[36] Further experimental studies are needed to identify mechanisms of the association between hot beverage drinking and ESCC.

Both black and green tea contain compounds with antioxidant activities (such as flavonoids), which might have the potential to reduce cancer risk.[2, 37] However, tea also contains several other compounds with unknown effects, and some potentially carcinogenic compounds may be introduced to tea when being processed (such as possible contamination of black tea with PAHs).[38] The number of prospective epidemiological studies on the association between amount of tea consumed and esophageal cancer risk is limited, and except for one showing an inverse association,[39] 4 studies have shown no association.[40–43] In analysis of the combined effects of measured temperature and amount in this study, the amount of tea

consumed appeared to be a factor only with drinking high-temperature tea. Our observation of statistically non-significant HRs above unity for drinking ≥1300 ml/day tea at <60°C may be due to some residual confounding from high tea temperature, as heavy tea drinkers in this study were more likely to drink tea at a higher temperature. However, we cannot entirely rule out an independent association between the amount of tea consumed and ESCC, because the number of individuals who drank tea at moderate temperatures was relatively modest in this study. Further, due to the lack of data, we were not able to incorporate in this analysis participants' preference for stronger or lighter tea or chemical composition of tea consumed. More research on the nature of these associations, including consideration of the heterogeneity of the chemical constituents of tea,[36] is needed.

The strengths of our study include its large size, prospective design, administration of structured questionnaires and physical measurement of tea temperature using a validated method by well-trained interviewers, low proportions of participants with missing data or lost to follow-up, accurate case ascertainment and confirmation, and adjustments for numerous potential confounders. In this study, the reference group included only those who drank tea, mostly in high amounts, which may provide stronger evidence on the association between tea drinking temperature and ESCC risk than when the reference group includes non-tea drinkers or those who drank tea infrequently,[6, 21] as the latter groups might have many other differences with regular, 'heavy' tea drinkers in terms of lifestyle factors, some of which might confound the association. It should be noted that we were not able to examine associations for drinking tea at lower amounts (<700 ml/day) or temperatures (e.g., 55–59°C) or for esophageal adenocarcinomas due to inadequate statistical power or study design, indicating the need for further research in other populations. Other limitations include the observational nature of the study leading to potential residual confounding (e.g., hot tea drinking as marker of other lifestyle factors), and the potential misclassification of exposure despite the effort to objectively quantify tea temperature. However, we adjusted our results for multiple known risk factors, and any substantial differential misclassification is unlikely.

Conclusions

In this prospective study, three independent measures of hot tea consumption, notably objectively measured temperature at baseline, were each associated with higher risk of ESCC, providing strong evidence for an association between hot beverage drinking and ESCC. High prevalence and high quantities of tea drinking at high temperatures could make the Golestan population considerably vulnerable to ESCC associated with drinking hot tea. As there is no known health benefit from drinking very hot beverages, it will be reasonable to advise people in Golestan and elsewhere to wait for their hot beverages to cool down before drinking. Further research is needed on mechanisms of this association, as well as associations between amount of tea consumed or drinking tea at more moderate temperatures and ESCC risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments.

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Novelty and Impact:

Our results from a unique setting (prospective measurement of tea temperature for more than 50,000 individuals) provides strong evidence supporting an association between hot beverage drinking and esophageal cancer. As there is no known health benefit from drinking very hot beverages, it will be reasonable to advise people in Golestan and elsewhere to wait for their hot beverages to cool down before drinking.

Table 1.

Baseline characteristics of Golestan Cohort Study participants according to the measured tea temperature

Baseline characteristics	Cohort baseline, *N*	Not a tea drinker %	<60°C, %	60–64°C, %	≥65°C, %	*P* value *
Total	49,996	1.1	38.9	38.4	21.6	–
Age						
Mean (SD) in years	52.1 (9.0)	53.4 (9.2)	51.6 (8.8)	52.0 (9.0)	53.2 (9.2)	<0.001
Sex						
Men	21,211	1.1	31.5	39.5	27.8	<0.001
Women	28,785	1.2	44.2	37.5	17.1	
Residence						
Rural	39,364	1.2	37.9	38.9	21.9	0.001
Urban	10,631	0.8	42.3	36.4	20.6	
Ethnicity						
Turkmen	37,223	1.1	39.6	37.8	21.6	<0.001
Non-Turkmen	12,773	1.3	36.8	40.2	21.7	
Education						
None	35,083	1.2	39.2	38.3	21.2	<0.001
1–8 years	10,700	0.9	37.0	39.3	22.8	
≥9 years	4,213	0.9	40.6	36.6	22.0	
Wealth score						
Third 1– lowest	16,320	1.4	38.0	38.4	22.2	<0.001
Third 2	17,096	1.1	38.0	38.6	22.4	
Third 3	16,580	0.9	40.6	38.2	20.3	
Fruit and vegetable intake						
Mean (SD) in g/day	337 (181)	285 (191)	336 (179)	335 (174)	345 (194)	0.017
Cigarette smoking						
Never	41,342	1.2	40.7	38.2	19.9	<0.001
Former	3,210	0.8	28.1	39.0	32.1	
Current	5,444	0.7	30.8	39.4	29.1	
Nass use						
Never	46,122	1.2	39.8	38.4	20.6	<0.001
Ever	3,874	0.6	27.5	38.4	33.6	
Opium ever use						
Never	41,516	1.2	40.5	38.3	20.0	<0.001
Ever	8,480	0.7	30.7	39.0	29.7	
Alcohol ever use						
Never	48,269	1.2	39.1	38.5	21.2	<0.001
Ever	1,727	0.6	30.8	35.5	33.1	

Due to missing data, the number of participants may not add up to the total number of participants included in this analysis. Percentages may not add up to 100% because of rounding.

* *P* values were calculated using a nonparametric K-sample test on the equality of medians for age and fruit and vegetable intake and analysis of variance (ANOVA) models for other variables. Those who did not drink tea were not included in calculation of *P* values, as they were not included in further analyses of tea temperature.

Table 2.

Association between tea drinking habits and risk of esophageal squamous cell carcinoma in the Golestan Cohort Study

Tea drinking habits	Cancer cases *N* (%)	Unadjusted HR (95% CI)	Adjusted HR1 (95% CI) *	Adjusted HR2 (95% CI) *
Measured tea temperature				
<60°C	92 (29.3)	1	1	1
≥60	222 (70.7)	1.60 (1.26–2.04)	1.42 (1.11–1.83)	1.41 (1.10–1.81)
60–64	135 (43.0)	1.52 (1.16–1.98)	1.45 (1.11–1.90)	1.44 (1.10–1.89)
≥65	87 (27.7)	1.75 (1.31–2.35)	1.38 (1.02–1.87)	1.36 (1.00–1.84)
P for trend		<0.001	0.029	0.039
Perceived tea temperature				
Cold or lukewarm	231 (73.6)	1	1	1
Hot	73 (23.3)	1.04 (0.80–1.36)	0.95 (0.73–1.24)	0.92 (0.70–1.21)
Very hot	10 (3.2)	3.48 (1.85–6.56)	2.44 (1.29–4.62)	2.41 (1.27–4.56)
P for trend		0.07	0.37	0.49
Self-reported time interval between tea being poured and drunk				
Continuous: per 2-minute shorter intervals (vs. ≥10 minutes)	314 (–)	1.26 (1.15–1.38)	1.11 (1.01–1.21)	1.10 (1.01–1.21)
Categorical:				
≥6 minutes	34 (10.8)	1	1	1
5 minutes	125 (39.8)	0.64 (0.45–0.89)	0.82 (0.58–1.16)	0.83 (0.59–1.17)
2 – 4 minutes	105 (33.4)	1.38 (1.07–1.79)	1.23 (0.94–1.60)	1.22 (0.94–1.59)
<2 minutes	50 (15.9)	2.21 (1.50–3.25)	1.53 (1.03–2.29)	1.51 (1.01–2.26)
P for trend		<0.001	0.002	0.003
Black tea amount				
0 – 599 ml/day	44 (14.3)	1	1	1
600 – 899	48 (15.6)	0.95 (0.63–1.43)	1.09 (0.72–1.65)	1.28 (0.83–1.98)
900 – 1199	54 (17.5)	1.33 (0.89–1.98)	1.28 (0.85–1.91)	1.50 (0.98–2.29)
1200 – 1599	80 (26.0)	1.38 (0.95–1.99)	1.36 (0.94–1.98)	1.61 (1.08–2.40)
≥1600	82 (26.6)	1.48 (1.03–2.14)	1.39 (0.96–2.03)	1.62 (1.08–2.43)
P for trend		0.005	0.042	0.013
Green tea amount				
0 ml/day	233 (75.7)	1	1	1
1 – 40	22 (7.1)	0.87 (0.56–1.34)	0.89 (0.57–1.38)	0.90 (0.58–1.40)
≥40	53 (17.2)	2.13 (1.58–2.87)	1.60 (1.17–2.19)	1.87 (1.34–2.61)
P for trend		<0.001	0.009	0.001
Tea amount (black and green)				
0 – 699 ml/day	48 (15.6)	1	1	1
700 – 999	45 (14.6)	1.46 (0.97–2.19)	1.60 (1.06–2.41)	1.59 (1.05–2.40)
1000 – 1299	68 (22.1)	1.46 (1.01–2.11)	1.43 (0.98–2.07)	1.40 (0.96–2.04)
1300 – 1699	66 (21.4)	2.08 (1.43–3.01)	1.71 (1.17–2.50)	1.67 (1.14–2.45)

Tea drinking habits	Cancer cases *N* (%)	Unadjusted HR (95% CI)	Adjusted HR1 (95% CI) *	Adjusted HR2 (95% CI) *
≥1700	81 (26.3)	2.04 (1.43–2.92)	1.70 (1.18–2.45)	1.64 (1.13–2.38)
P for trend		<0.001	0.006	0.014

CI, confidence interval; HR, hazard ratio.

Due to missing data, the number of participants may not add up to the total number of participants included in this analysis. Percentages may not add up to 100% because of rounding. *P* values for trend are from the same models in which consecutive integers were assigned to consecutive categories of each variable.

* HR3s are adjusted for age at baseline, sex, urban-rural residence, ethnicity, education level, wealth score, fresh fruit and vegetable consumption (on a logarithmic scale), cigarette smoking, nass chewing, opium use, and alcohol consumption. HR2 are adjusted for the same variables as HR1s, plus some tea drinking variables: measured and perceived temperature and interval variables were additionally adjusted for black tea and green tea consumption, and tea consumption variables were additionally adjusted for the measured tea temperature (≥60°C, 60–64°C, and ≥65°C), and black tea and green tea consumption were also adjusted for the consumption of the other type of tea.

Table 3.

Combined effect of tea drinking temperature and amount on risk of esophageal squamous cell carcinoma among tea drinkers in the Golestan Cohort Study

	Measured temperature					
	<60°C			≥60°C		
Tea drinking amount (black and green)	**Cancer cases *N***	**Unadjusted HR (95% CI)**	**Adjusted HR (95% CI) ***	**Cancer cases *N***	**Unadjusted HR (95% CI)**	**Adjusted HR (95% CI) ***
5 categories						
1 – 699 ml/day	18	1	1	27	1.28 (0.70–2.32)	1.10 (0.61–2.00)
700 – 999	11	0.97 (0.46–2.04)	1.01 (0.48–2.14)	34	2.26 (1.28–4.00)	2.15 (1.21–3.81)
1000 – 1299	15	0.97 (0.49–1.92)	0.91 (0.46–1.81)	53	2.17 (1.27–3.70)	1.84 (1.08–3.15)
1300 – 1699	20	1.96 (1.04–3.71)	1.59 (0.84–3.01)	46	2.70 (1.56–4.65)	1.93 (1.11–3.34)
≥1700	23	2.10 (1.13–3.89)	1.73 (0.93–3.21)	58	2.51 (1.48–4.26)	1.83 (1.07–3.13)
3 categories						
1 – 699 ml/day	18	1	1	27	1.28 (0.70–2.32)	1.10 (0.61–2.00)
700 – 1299	26	0.97 (0.53–1.76)	0.95 (0.52–1.74)	87	2.20 (1.33–3.66)	1.95 (1.17–3.25)
≥1300	43	2.03 (1.17–3.53)	1.66 (0.95–2.89)	104	2.59 (1.57–4.27)	1.87 (1.13–3.11)

CI, confidence interval; HR, hazard ratio.

Due to missing data, the number of participants may not add up to the total number of participants included in this analysis.

* HRs are adjusted for age at baseline, sex, urban-rural residence, ethnicity, education level, wealth score, fresh fruit and vegetable consumption (on a logarithmic scale), cigarette smoking, nass chewing, opium use, and alcohol consumption.