RESEARCH

Tea drinking habits and oesophageal cancer in a high risk area in northern Iran: population based case-control study

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ABSTRACT

Objective To investigate the association between tea drinking habits in Golestan province, northern Iran, and risk of oesophageal squamous cell carcinoma.

Design Population based case-control study. In addition, patterns of tea drinking and temperature at which tea was drunk were measured among healthy participants in a cohort study.

Setting Golestan province, northern Iran, an area with a high incidence of oesophageal squamous cell carcinoma.

Participants 300 histologically proved cases of oesophageal squamous cell carcinoma and 571 matched neighbourhood controls in the case-control study and 48 582 participants in the cohort study.

Main outcome measure Odds ratio of oesophageal squamous cell carcinoma associated with drinking hot tea.

Results Nearly all (98%) of the cohort participants drank black tea regularly, with a mean volume consumed of over one litre a day. 39.0% of participants drank their tea at temperatures less than 60°C, 38.9% at 60-64°C, and 22.0% at 65°C or higher. A moderate agreement was found between reported tea drinking temperature and actual temperature measurements (weighted κ 0.49). The results of the case-control study showed that compared with drinking lukewarm or warm tea, drinking hot tea (odds ratio 2.07, 95% confidence interval 1.28 to 3.35) or very hot tea (8.16, 3.93 to 16.9) was associated with an increased risk of oesophageal cancer. Likewise, compared with drinking tea four or more minutes after being poured, drinking tea 2-3 minutes after pouring (2.49, 1.62 to 3.83) or less than two minutes after pouring (5.41, 2.63 to 11.1) was associated with a significantly increased risk. A strong agreement was found between responses to the questions on temperature at which tea was drunk and interval from tea being poured to being drunk (weighted κ 0.68).

Conclusion Drinking hot tea, a habit common in Golestan province, was strongly associated with a higher risk of oesophageal cancer.

INTRODUCTION

Oesophageal squamous cell carcinoma constitutes most of the oesophageal cancers worldwide.[1 2] In Europe and America it is mainly caused by tobacco and alcohol use and is more common in men than in women.[3] However, in Golestan province of Iran, which has one of the highest incidence rates for oesophageal squamous cell carcinoma in the world,[4] this cancer has relatively unique epidemiological features: smoking and alcohol consumption are not major risk factors[5 6] and women are as likely to have a diagnosis of oesophageal cancer as men.[7] This epidemiological pattern resembles that observed in Linxian, China, another area with a high incidence of oesophageal squamous cell carcinoma.[8] Earlier studies in Golestan have suggested that low intake of fresh fruits and vegetables, low socioeconomic status, and opium consumption are associated with a higher risk of oesophageal cancer.[5 6] In addition, studies have pointed towards the possible role of drinking very hot tea.[9]

An association between drinking hot beverages and risk of oesophageal cancer has been reported in several studies from different parts of the world.[3 10-14] In Golestan, tea and water are the only drinks commonly consumed, with comparable average intake.[15] An ecological study showed that inhabitants of Golestan drank more tea and at a higher temperature than people living in a nearby area with a low incidence of oesophageal cancer.[16] A case-control study carried out in areas of both low and high incidence in northern Iran in the 1970s showed about a twofold increase in risk of oesophageal cancer among people who drank hot tea, but there was no trend in risk according to quantity of tea consumed.[5]

In contrast with some other risk factors, such as opium consumption, which may affect only a fraction of the general population or may have dissimilar distributions among men and women, tea drinking in Golestan is widespread in both sexes, usually starts at

an early age, and continues for life. Therefore drinking hot tea could potentially be an important risk factor for oesophageal squamous cell carcinoma in this area. We collected questionnaire data in a case-control study of histologically proved cases of oesophageal squamous cell carcinoma in high incidence areas of Golestan to investigate the association between tea drinking habits and risk of oesophageal cancer. We also measured the usual temperature at which tea was drunk and collected questionnaire data on tea drinking habits in a large scale cohort study in Golestan. We report the results of the case-control study and also tea drinking patterns among 48 582 healthy participants within the cohort study.

METHODS

A detailed description of the design and methods of the case-control study is available elsewhere.[6-17] Briefly, the study was carried out in the eastern part of Golestan province, northern Iran. Case participants were recruited between December 2003 and March 2007 at Atrak Clinic, the only gastrointestinal specialty clinic in the study area. Doctors in the study catchment area were asked to refer any patients suspected of having cancers of the upper gastrointestinal tract to Atrak Clinic, where all the patients underwent video oesophagogastroduodenoscopy. Patients with suspicious lesions in the oesophagus during endoscopy were invited to participate in the study; nearly all of those who were invited participated. Fixed biopsy samples were sent to the Tehran University Digestive Disease Research Center, where they were examined by experienced pathologists. Only newly diagnosed patients with histologically confirmed oesophageal cancer were finally included as case participants in the study. Cancer registry data show that nearly 70% of all incident cases of oesophageal cancer in this area were enrolled in the case-control study (unpublished data). For each case participant we tried to select two population based controls matched to the cases on place of residence, age (SD 2 years), and sex, using data from a family health census that is carried out by the Iranian primary healthcare system and is updated annually. A roster of eligible controls was prepared for each case, from which the controls were selected at random. If the first randomly selected control did not agree to participate, the second person was approached, and so on. Most of the selected controls agreed to participate; of the enrolled controls 77% were the first randomly selected patients and 11% the second. In nearly all instances in which selected patients were not enrolled, the reason for not participating was the absence of an eligible control at the time of invitation. Written consent was obtained from all participants.

Using a structured questionnaire trained interviewers collected information on personal characteristics, several other potential confounders of interest, and tea drinking temperature in face to face interviews. The participants were asked whether they drank tea and, if so, whether they usually drank it warm, lukewarm, hot, or very hot. They were also questioned about the interval (in minutes) between tea being poured and drunk. We asked separately about consumption of black and green tea, using a food frequency questionnaire specifically designed for this population[18]; this questionnaire was administered by a trained nutritionist. For this we asked participants about the usual frequency of drinking tea and the volume of the cups usually used. We provided photographs of five types of cups and mugs that are commonly used in the study area. A limited number of staff carried out the interviews and no proxies were used. For cases, the questions referred to the period before symptoms began. Case participants were interviewed on the same day that they underwent diagnostic endoscopy of the upper gastrointestinal tract at Atrak Clinic.

The Golestan Cohort Study is a prospective study that recruited 50 045 adults, aged 40-75, from Golestan

Table 1 | Characteristics of patients with oesophageal squamous cell carcinoma (cases) and matched controls* in Golestan, northern Iran, 2003-7. Values are numbers (percentages) of participants unless stated otherwise

Characteristic	Cases (n=300)	Controls (n=571)	P value†
Mean (SD) age (years)	64.5 (10.1)	64.3 (10.4)	0.81
Men	150 (50.0)	278 (48.6)	
Women	150 (50.0)	293 (51.4)	0.70
Area of residence:			
Urban	82 (27.3)	150 (26.3)	
Rural	218 (72.7)	421 (73.7)	0.77
Duration of residence in rural areas (years):			
0	9 (3.0)	29 (5.1)	
1-20	26 (8.7)	51 (8.9)	0.36
>20	264 (88.3)	491 (86.0)	
Ethnicity:			
Turkmen	171 (57.0)	312 (54.6)	
Non-Turkmen	129 (43.0)	259 (45.4)	0.64
Education:			
No school	267 (89.0)	474 (83.0)	
Primary school	25 (8.3)	64 (11.2)	0.04
Middle school or higher	8 (2.7)	33 (5.8)	
Car ownership:			
No	252 (84.3)	461 (75.6)	
Yes	47 (15.7)	139 (24.4)	0.003
Alcohol ever use:			
No	292 (97.7)	553 (97.4)	
Yes	7 (2.3)	15 (2.6)	0.86
Tobacco‡ and opium use:			
Neither	166 (55.5)	398 (69.8)	
Tobacco	43 (14.4)	66 (11.6)	
Opium	30 (10.0)	34 (6.0)	0.0002
Both	60 (20.1)	72 (12.6)	

As a result of missing data, the number of cases and controls for some variables may be less than 300 and 571, respectively.
*Although cases and controls were individually matched, percentages of either are not necessarily equal in each category for sex or area of residence as some cases had one matched control and others had two.
†χ² tests for categorical variables (χ² for trend in variables with more than two categories) and Wilcoxon rank sum test for continuous variables.
‡Any kind of tobacco consumption, including cigarette, pipe, and hookah (water pipe) and chewing nass (a mixture of tobacco, lime, and ash).

province between January 2004 and June 2008. A total of 16 599 inhabitants in the specified age range were selected randomly from Gonbad City, the main urban area in eastern Golestan, by systematic clustering based on the household number. In rural areas, all residents of villages in the study catchment area in the specified age range were invited to participate. Eligible participants were enrolled in the study unless they were unwilling to participate at any stage for any reason, were temporary residents, or had a current or previous diagnosis of an upper gastrointestinal cancer. In urban areas, 10 032 participants were enrolled, with participation rates of about 70% for women and 50% for men. In rural areas, 40 013 participants were enrolled from 326 villages, with participation rates of 84% for women and 70% for men.

The same questions for tea temperature were asked as in the case-control study. In addition we measured the temperature of tea drunk by the participants. To achieve this we prepared a fresh cup of tea for each participant and measured the temperature of the tea using a digital thermometer. When the temperature was 75°C we asked the participants to sip the tea and say whether that was the temperature at which they usually drank tea. If not, the tea was allowed to cool to 70°C and the question was asked again. This procedure was repeated, at 5°C intervals, until the temperature at which tea was usually drunk was reached. This

method for measuring the temperature of tea showed good reliability when tested in the pilot phase of the cohort study.[19]

Statistical analysis

The usual interval between tea being poured and drunk was categorised as four or more minutes, 2-3 minutes, and less than two minutes. Within the case-control study the amount of black tea consumed each day (millilitres) was categorised into fifths. For green tea, however, because only a small number of participants drank this kind of tea, we present only the frequency of consumption. Data on tea temperature were available for over 99% of cases and of controls. The amount of tea, however, was available for 89% of the cases and 67% of the controls. We excluded participants with missing data on a variable from the corresponding analysis. Conditional logistic regression was used to calculate odds ratios and corresponding 95% confidence intervals. By design, case and control participants were matched for age, sex, and place of residence. We used logistic regression models to adjust for potential confounders, including ethnicity, daily vegetable intake, alcohol consumption, tobacco or opium use, duration of residence in rural areas, education level, and car ownership, as indicators of socioeconomic status, and other tea drinking variables. P values for trend were obtained from adjusted

Table 2 | Distribution of usual tea drinking habits and corresponding odds ratios (95% CIs) among 300 cases with oesophageal squamous cell carcinoma and 571 matched controls, in Golestan, northern Iran, 2003-7. Values are numbers (percentages) of participants unless stated otherwise

Variables	Cases (n=300)	Controls (n=571)	Crude odds ratio (95% CI)	Adjusted odds ratio* (95% CI)	P value for trend†
Tea temperature:					
Warm or lukewarm	127 (42.6)	394 (69.4)	1.00	1.00	
Hot	108 (36.2)	155 (27.3)	2.14 (1.52 to 3.01)	2.07 (1.28 to 3.35)	‹0.001
Very hot	63 (21.1)	19 (3.3)	9.33 (5.26 to 16.56)	8.16 (3.93 to 16.91)	
Interval between tea being poured and drunk (minutes):					
≥4	132 (44.3)	394 (69.5)	1.00	1.00	
2-3	112 (37.6)	138 (24.3)	2.32 (1.68 to 3.23)	2.49 (1.62 to 3.83)	‹0.001
‹2	54 (18.1)	35 (6.2)	4.03 (2.50 to 6.49)	5.41 (2.63 to 11.14)	
Amount of black tea consumed (ml/day):					
0-675	48 (18.0)	81 (21.0)	1.00	1.00	
676-920	40 (15.0)	75 (19.5)	0.85 (0.46 to 1.58)	0.91 (0.43 to 1.91)	
921-1215	37 (13.9)	86 (22.3)	0.68 (0.38 to 1.23)	0.68 (0.34 to 1.37)	0.03
1216-1725	65 (24.3)	70 (18.2)	1.57 (0.89 to 2.75)	1.46 (0.75 to 2.86)	
≥1726	77 (28.8)	73 (19.0)	1.86 (1.07 to 3.23)	1.83 (0.93 to 3.59)	
Frequency of green tea consumption:					
Never, ‹weekly	249 (93.6)	356 (92.2)	1.00	1.00	
Daily, weekly	17 (6.4)	30 (7.8)	0.65 (0.32 to 1.31)	0.89 (0.38 to 2.09)	0.82

Because of missing data and one participant who did not drink tea, number of cases and controls for some variables may be less than 300 and 571, respectively.

*Adjusted for ethnicity (non-Turkmen or Turkmen), daily vegetable intake (logarithmic scale), alcohol consumption (never or ever), tobacco or opium ever use (none, only tobacco, only opium, or both), duration of residence in rural areas (0, 1-20 years, or ›20 years), education level (no school, primary school, or middle school or higher), car ownership (no or yes), and variables listed in table, excluding interval variable; interval variable was not adjusted for tea temperature.

†P values come from adjusted conditional logistic regression models in which consecutive integers were assigned to consecutive categories of each variable.

Table 3 | Comparison of questionnaire data on tea temperature among 300 cases with oesophageal squamous cell carcinoma and 571 matched controls, in Golestan, northern Iran, 2003-7

Interval (minutes)*	Tea temperature			Weighted κ statistics (SE)	Correlation coefficient† (P value)
	Warm or lukewarm	Hot	Very hot		
≥4	454	65	7		
2-3	57	163	30	0.68 (0.03)	0.69 (<0.001)
<2	8	35	45		

Because of missing data and one participant who did not drink tea, numbers add up to 864 rather than 871.
*Interval between tea being poured and drunk.
†Spearman's rank correlation coefficient.

conditional logistic regression models by assigning consecutive numbers to categories within each categorical variable. We tested the agreement between tea temperature categories and the interval between tea being poured and drunk by weighted κ statistics and Spearman's rank correlation coefficients.

Less than 3% of the cohort participants had one or more missing values in tea drinking variables. These participants were excluded from the current analyses. We calculated means and standard deviations for daily intake of black and green tea among the cohort participants and the percentage of participants who drank these two kinds of tea daily, weekly, or less. In addition, we examined the validity of the questionnaire data on tea temperature within the cohort study. For this we categorised tea temperature measurements as less than 65°C, 65-69°C, and 70°C or more, because their distribution was close to that of the categorical variable used in the questionnaire. We then compared them with the questionnaire data, using weighted κ statistics and Spearman's rank correlation coefficients.

The methods of sample size calculation for both studies are presented in the web extra. Throughout the

analyses we considered two sided P values <0.05 as significant. All statistical analyses were done using Stata version 10.0 software.

RESULTS
Case-control study
A total of 300 cases and 571 controls were recruited into the study. All cases had at least one matched control. The personal characteristics of the cases and controls were similar (table 1).

Only one participant did not drink tea. Tea temperature was significantly associated with risk of oesophageal squamous cell carcinoma (table 2). Compared with drinking warm or lukewarm tea, drinking hot tea (odds ratio 2.07, 95% confidence interval 1.28 to 3.35) or very hot tea (8.16, 3.93 to 16.91) was associated with an increased risk of oesophageal cancer (P for trend <0.001). The risk associated with drinking hot tea did not vary by education level or several other personal variables (see web extra table). The interval between tea being poured and drunk was inversely associated with risk of oesophageal cancer (table 2). Compared with an interval of four or more minutes, intervals of 2-3 minutes (odds ratio 2.49, 95% confidence interval 1.62 to 3.83) and less than two minutes (5.41, 2.63 to 11.14) were associated with an increased risk of oesophageal cancer (P for trend <0.001). The weighted κ statistic and Spearman's rank correlation coefficient for agreement between these two variables were 0.68 and 0.69, respectively (table 3). A similar agreement was observed within the case and control groups and among men and women separately (data not shown). Information on amount of tea drunk was available for only 267 cases and 385 controls. No clear pattern of association was found between the amount of black tea consumed and risk of cancer in crude or multivariate analyses, but the trend test was statistically

Table 4 | Usual mean daily amount and frequency of tea drinking among 48 582 participants in Golestan Cohort Study, Golestan, northern Iran, 2004-8. Values are percentages of participants unless stated otherwise

Characteristics	Total No	Black tea				Green tea			
		Mean (SD) volume (ml/day)	Frequency of consumption			Mean (SD) volume (ml/day)	Frequency of consumption		
			Daily	1-6 days a week	Never, <weekly		Daily	1-6 days weekly	Never, <weekly
Total	48 582	1179 (761)	96.8	0.6	2.6	48 (228)	5.8	4.7	89.5
Men	20 649	1306 (869)	97.3	0.5	2.2	41 (218)	4.8	4.2	91.0
Women	27 933	1085 (655)	96.5	0.6	2.9	52 (235)	6.5	5.2	88.3
Area of residence:									
Urban	9949	1182 (823)	98.0	0.7	1.3	37 (179)	6.0	7.0	87.0
Rural	38 633	1178 (745)	96.5	0.5	3.0	50 (239)	5.7	4.2	90.1
Ethnicity:									
Non-Turkmen	12 610	1186 (749)	99.0	0.3	0.7	6 (77)	0.9	1.0	98.1
Turkmen	35 972	1176 (765)	96.1	0.6	3.3	62 (260)	7.5	6.1	86.4
Formal education:									
None	33 990	1158 (720)	96.4	0.5	3.1	53 (245)	6.2	4.7	89.1
Primary school	8253	1225 (813)	97.9	0.5	1.6	37 (195)	4.6	4.5	90.9
Middle school	2205	1239 (884)	97.6	0.8	1.5	34 (178)	4.4	4.5	91.1
High school	3095	1246 (913)	98.0	0.6	1.4	31 (150)	4.8	5.6	89.6
College or university	1039	1151 (830)	98.0	1.0	1.0	46 (188)	7.4	7.4	85.2

Table 5 | Usual tea drinking temperature among 48 582 participants in Golestan Cohort Study, Golestan, northern Iran, 2004-8. Values are percentages of participants unless stated otherwise

Characteristics	Total No	Temperature (°C)				
		Never	<60	60-64	65-69	≥70
Total	48 582	0.1	39.0	38.9	16.6	5.4
Men	20 649	0.2	31.6	40.0	20.3	7.9
Women	27 933	0.1	44.5	38.1	13.7	3.6
Area of residence:						
Urban	9949	0.1	42.2	36.6	15.7	5.4
Rural	38 633	0.1	38.2	39.5	16.8	5.5
Ethnicity:						
Non-Turkmen	12 610	0.3	37.2	40.6	16.7	5.2
Turkmen	35 972	0.1	39.6	38.3	16.5	5.5
Formal education:						
None	33 990	0.1	39.4	38.8	16.5	5.2
Primary school	8253	0.1	37.4	39.7	16.9	5.9
Middle school	2205	0.4	35.7	39.9	16.8	7.2
High school	3095	0.2	38.7	38.1	17.1	5.9
College or university	1039	0.2	46.2	33.5	14.5	5.6

significant (P value for trend 0.03). There was no statistically significant association between frequency of green tea consumption and risk of cancer.

Cohort study

Data on tea drinking variables were available for 48 582 cohort participants. Almost all (96.8%) of the participants drank black tea every day (47 043 participants), with a mean amount of 1179 ml (SD 761) a day. Only 2802 participants (5.8% of all participants) drank green tea every day; most of them were of Turkmen ethnicity. The mean amount of green tea consumption was 48 ml (SD 228) a day (table 4). Overall, 18 947 (39.0%) participants drank their tea at temperatures less than 60°C, 18 889 (38.9%) at 60-64°C, and 10 688 (22.0%) at 65°C or higher (table 5).

The weighted κ statistic and Spearman's rank correlation coefficient for agreement between reported tea drinking temperature and actual temperature measurements were 0.49 and 0.46, respectively (table 6). The corresponding values for agreement between actual measurements and the interval between tea being poured and drunk were 0.39 and 0.32, respectively.

DISCUSSION

Our study found that almost everyone in Golestan Province drinks tea. They drink large amounts of black tea every day, but drinking green tea is not common. We found a strong increase in the risk of oesophageal squamous cell carcinoma associated with drinking hot or very hot tea but not with the amount of tea consumed, which is consistent with the previous literature.[3]

Compared with rats that received only carcinogenic N-nitroso compounds or hot water, the mean number of benign and malignant oesophageal tumours significantly increased in rats that received both N-nitroso compounds and hot water.[20 21] In one of these studies,[21] in which hot water was administered by installation in the upper section of the oesophagus, more tumours were observed as the temperature increased, especially at 65°C and above. At a temperature of 70°C the number and size of oesophageal papillomas increased rapidly.[21] A few studies have investigated the effect of hot beverages on intra-oesophageal temperature in humans.[22 23] One study showed that after drinking beverages with temperatures up to 65°C, distal oesophageal temperature increased to as high as 53°C.[23] The volume swallowed in each sip was more important than the temperature of the beverage in determining intraoesophageal temperature.[23] In our study we asked the participants if they sipped or gulped their tea, but we did not analyse these data because few participants gulped their tea. In addition, we did not find a good way to validate the answers to this question. The volume swallowed in each sip may differ from person to person, and a given volume may be divided in two or more quick swallows.

Possible mechanistic pathways

The mechanism by which thermal injury can cause oesophageal cancer is not clear but both direct and indirect effects have been suggested. Some authors have proposed that inflammatory processes associated with chronic irritation of the oesophageal mucosa by local hyperthermia might stimulate the endogenous formation of reactive nitrogen species, such as nitric oxide, and subsequently, N-nitroso compounds.[24] Consistent with this idea, higher rates of transitions of somatic G to A in CpG dinucleotides of the *TP53* gene have been reported in samples of oesophageal tumour from areas in which drinking hot beverages is considered an important risk factor for oesophageal cancer,[25-28] and an association between these mutations and nitric oxide synthase activity has been reported in colorectal cancers in humans.[29] Thermal injury can also impair the barrier function of the oesophageal epithelium, which may increase the risk of damage

from exposure to intraluminal carcinogens[20 21 30] such as polycyclic aromatic hydrocarbons or the compounds present in opium dross. The population of Golestan is highly exposed to polycyclic aromatic hydrocarbons, most probably through diet.[31 32] Threshold temperatures have been suggested for the effect of hot beverages on the epithelial barrier of the oesophagus in rabbits (intraluminal temperature of 49°C for epithelium permeability and of 60°C for active ion transport). Once the threshold temperature is reached, the barrier function could be impaired rapidly and with short exposure times.[30] Whatever the mechanism by which thermal injury increases the risk of oesophageal cancer, this risk can be augmented by other risk factors, such as low intake of fresh fruits and vegetables, which can impair DNA repair.[33]

Both green and black teas have shown cancer prevention activity in animal models, which may be attributable to flavonoids and other beneficial compounds[34-36]; however, such activity has not been convincingly shown in humans.[37 38] After adjustment for tea temperature and other factors we did not find a clear pattern of association between the amount of tea consumed and the risk of oesophageal cancer. Although the P value for trend for this association was statistically significant, the risk decreased from the first to the third fifths and then increased, so there was no consistent pattern. In contrast with tea, which is possibly carcinogenic only if it is drunk at high temperatures,[3] drinking maté, a herbal infusion consumed in certain areas of South America, may increase the risk of oesophageal cancer even at low temperatures.[12 39] This increased risk may be due to carcinogens that are produced during the processing of the herbal leaves, such as polycyclic aromatic hydrocarbons, or to other compounds present in the unprocessed leaves.[40 41]

Comparison with other studies

The results of the cohort study showed that most inhabitants of Golestan drink their tea at temperatures higher than 60°C and in quantities greater than one litre a day. These patterns make the Golestan population particularly vulnerable to the possible carcinogenic effects of drinking hot tea. Several previous studies have assessed temperature preferences for beverages, and those from the United Kingdom have reported an average temperature preference of 56-60°C among healthy populations.[16 22 42-45] One study reported a significantly higher tea drinking temperature among seven participants with oesophageal disorders (mean 62°C, range 53-73°C) than among 50 controls (mean 56°C, range 47.5-65°C, P<0.001).[43] Another study reported a mean temperature of 69.5°C (SD 6.5°C) for drinking maté among 1388 inhabitants in southern Brazil, a moderate to high incidence area for oesophageal squamous cell carcinoma.[44]

The association between drinking hot beverages and risk of oesophageal cancer suggests that thermal injury could be a cause of other cancers of the upper aerodigestive epithelial; however, this hypothesis has been investigated in only a few epidemiological studies. For hot tea drinking, the evidence is too limited to draw any conclusions.[46-48] All of the six studies that investigated maté drinking and cancer of the mouth, pharynx, and larynx showed an association with hot maté intake, which was statistically significant in four studies.[48] Potential carcinogenic effects of hot beverages on other parts of the upper aerodigestive tract warrant further investigations.

Strengths and limitations of the study

To our knowledge the Golestan Cohort Study is the largest epidemiological study in which tea drinking temperature has been measured. The measurement method was validated in the pilot phase of this study[19] and all measurements were done by trained staff. The strengths of our case-control study include histological verification of all cases of oesophageal squamous cell carcinoma, administration of a structured questionnaire by well trained interviewers, and adjustment for potential confounders. Furthermore, with no or minimal confounding from alcohol or tobacco use in Golestan, other risk factors for oesophageal cancer can be better studied there. As in all case-control studies, however, data on the amount and temperature of consumed tea can be subject to information

Table 6 | Agreement between tea temperature variables among 48 582 participants in Golestan Cohort Study, Golestan, northern Iran, 2004-8

Descriptive variables	Measured temperatures			Weighted κ statistic (SE)	Spearman's rank correlation coefficient (P value)
	<65°C	65-69°C	≥70°C		
Tea temperature:					
Warm or lukewarm	32 414	3749	467		
Hot	5385	4246	1757	0.49 (0.005)	0.46 (<0.001)
Very hot	37	48	421		
Interval between tea being poured and drunk (minutes)					
≥4	30 259	4678	675		
2-3	6836	2691	859	0.39 (0.005)	0.32 (<0.001)
<2	741	674	1111		

Participants who did not drink tea were not included in these analyses, therefore total number of participants is 48 524.

bias. We found good agreement between questions on the temperature that tea was drunk and the interval between tea being poured and drunk, but responses to both questions could have been biased. The validation study in the cohort was carried out among healthy people, so the observed acceptable validity may not be applicable to case participants. Studies in the Caspian littoral in the 1970s suggested that drinking hot beverages may be a possible risk factor for oesophageal squamous cell carcinoma, so the hypothesis might be familiar to the interviewers and people of the study area; however, we are not aware of any public educational programme in this regard. We tried to minimise the risk of information bias by not discussing the study hypotheses with the interviewers. The questionnaires were fairly extensive, studying multiple hypotheses, which reduced the possibility of interviewers' focusing on a certain hypothesis. Also, we did not observe any evidence of inflated results for other known risk factors for oesophageal cancer, such as tobacco smoking or alcohol consumption, which further suggests that severe information bias is not highly likely.[6] Case participants with no formal education might be less likely to be aware of the study hypotheses, so they might be less prone to recall bias. In our sensitivity analyses we found no substantial difference in the risk associated with hot tea drinking between participants with and without formal education, or between urban and rural areas. Another problem with a case-control design is selection bias. Since ascertainment of cases and controls in our study was high, selection bias may only explain our findings if the small proportion of non-participating cases were overwhelmingly drinkers of "cold tea" or, conversely, the non-participating controls were overwhelmingly drinkers of "hot tea." None of the scenarios are likely. In our study the amount of missing data on the variable for amount of tea drinking varied between cases and controls, which was due to a logistical issue rather than bias. The questions on amount of tea drunk came from a nutritional questionnaire that was administered by a nutritionist. On some days no nutritionist was available to accompany the control selection team and therefore this variable has some missing data. Since we used conditional logistic regression models, in which each case is compared with their matched controls, the missing values are not expected to differentially distort our findings even if there are some differences in the personal characteristics of participants with or without missing values. Despite the presence of the missing data, we report the results of amount of tea consumed in relation to the risk of oesophageal squamous cell carcinoma because even after excluding the participants with missing values, our study is still one of the largest that have reported on this association. Overall, we believe that the strong association between drinking hot tea and risk of oesophageal cancer found in this study is unlikely to be completely due to bias, considering its agreement with the previous literature and our efforts to collect accurate and valid data. Nonetheless, we acknowledge that the nature and strength of the association needs to be established in prospective studies.

Conclusions and policy implications

Our results showed a noticeable increase in risk of oesophageal squamous cell carcinoma associated with drinking tea hot. A large proportion of Golestan inhabitants drink hot tea, so this habit may account for a substantial proportion of the cases of oesophageal cancer in this population. Informing the population about the hazards of drinking hot tea may be helpful in reducing the incidence of oesophageal cancer in Golestan and in other high risk populations where similar habits are prevalent.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Heavy alcohol and tobacco use are major risk factors for oesophageal squamous cell carcinoma, a disease more common in men than women

In some areas with a high incidence of oesophageal cancer, alcohol and tobacco use are not prominent risk factors, and women are as likely to develop oesophageal cancer as men

Common risk factors among both sexes may have a role in the carcinogenesis of oesophageal cancer; drinking hot beverages is a suggested risk factor

WHAT THIS STUDY ADDS

The risk of oesophageal cancer was noticeably increased in adults in Golestan Province, northern Iran, who drank tea hot

Drinking hot beverages is common and may account for a substantial number of cases of oesophageal squamous cell carcinoma, especially in areas with a high incidence

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