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ORIGINAL RESEARCH

Esophageal Carcinoma and Associated Risk Factors: A Case-control Study in Two Tertiary Care Hospitals of Kabul, Afghanistan

Ramin Saadaat[1], Jamshid Abdul-Ghafar[1], Ahmed Maseh Haidary[1], Nooria Atta[2], Tazeen Saeed Ali[3]

[1]Department of Pathology and Clinical Laboratory, French Medical Institute for Mothers and Children (FMIC), Kabul, Afghanistan; [2]Department of Gynecology and Obstetrics, Kabul University of Medical Science (KUMS), Kabul, Afghanistan; [3]School of Nursing and Midwifery and Department of Community Health Sciences, Aga Khan University (AKU), Karachi, Pakistan

Correspondence: Jamshid Abdul-Ghafar, Department of Pathology and Clinical Laboratory, French Medical Institute for Mothers and Children (FMIC), Kabul, Afghanistan, Tel +93 792 827287, Email jamshid.jalal@fmic.org.af

Purpose: Esophageal cancer (EC) is the most common cancer among males in Afghanistan, thus we aimed to conduct a case-control study to determine the associated risk factors with EC in two tertiary care hospitals of Kabul, Afghanistan.

Patients and Methods: We enrolled 132 EC cases and 132 controls and used conditional logistic regression to estimate the odds ratio (OR) with consideration of 95% confidence interval (CI).

Results: The results of our study revealed that esophageal squamous cell carcinoma (ESCC) was the predominant type of EC constituting 75.8% of the cases. The results of the multivariate logistic analysis showed that males and older ages were at increased risk of developing EC (OR: 4.62, 95%CI, *p*-value=0.026) and (OR: 1.070, 95%CI, *p*-value <0.001), respectively. In addition, living in rural areas (OR: 46.64, 95%CI, *p*-value <0.001), being uneducated (OR: 13.94, 95%CI, *p*-value=0.042), using oral snuff (OR: 6.10, 95%CI, *p*-value=0.029), drinking hot tea (OR: 5.719, 95%CI, *p*-value=0.005), lack of physical exercise (OR: 32.548, 95%CI, *p*-value=0.001), less fresh fruit consumption (OR: 93.18, 95%CI, *p*-value<0.001) and family history of cancer (OR: 14.50, 95%CI, *p*-value=0.003) were significantly associated with the development of EC, while body mass index (BMI), smoking, alcohol drinking, consumption of spicy food and pickled vegetables did not have a significant association with EC. Moreover, the majority of the cases (83.3%) in our study were from to low-income families and the majority were unemployed (93.9%), of whom (50%) were farmers, who did not show statistically significant association.

Conclusion: Our study concluded that EC risk was higher in older ages, males, rural residents, uneducated people, oral-snuff users, hot tea drinkers, fewer fresh fruit consumers, lack of physical exercise, and family history of cancer. Further detailed studies and screening policies of the affected groups are suggested to further elaborate on the subject.

Keywords: esophageal cancer, squamous cell carcinoma, adenocarcinoma, risk factors, sociodemographic, family history

Introduction

Noncommunicable diseases are rapidly increasing worldwide and are now responsible for the majority of deaths globally. The vast majority of noncommunicable diseases are attributed to cancers.[1] Esophageal cancer (EC) is the seventh most common cancer in terms of incidence and sixth most common cancer in terms of cancer-related death worldwide. In 2018 alone, 572,000 new cases were diagnosed, and overall, 509,000 deaths were estimated globally.[2] In Afghanistan, no nationwide cancer study has ever been conducted to demonstrate the incidence and mortality rate of EC except for a single center study, in which it was estimated that EC was most common cancer in males and the second most common cancer in females.[3]

EC arises from surface lining cells of the esophageal mucosa. There are two main histologic patterns of EC,[1] esophageal squamous cell carcinoma (ESCC) and[2] esophageal adenocarcinoma (EAC).[4] International Agency for Research on Cancer (IARC) estimated that ESCC comprised 88% of all EC and the remaining 12% were EAC.[5] The

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incidence rates and histological subtypes of EC differ significantly by geographic region. Although, ESCC is the most common type of EC worldwide, but EAC is more common in Western nations. In developed world, EAC is rapidly rising to the top spot for EC.[6]

The incidence rate of EC is different among different parts of the world, even two areas 100 miles apart have been estimated to have a significant variation in the incidence rates of EC.[7] Many risk factors have been identified to be related to the development of EC, including male gender, race, obesity, smoking, alcohol consumption, hot beverages, nutritional deficiencies, genetic susceptibility, and gastroesophageal reflux disease.[8] Alcohol consumption and cigarette smoking are well-established risk factors for the development of EC, and studies have demonstrated synergistic effect of various risk factors on EC.[9] In contrast, fresh fruit intake and physical exercise have been demonstrated to have a protective role against EC.[9]

The causes of ESCC are multifactorial and therefore dependent on the population. A study conducted in the United States (US) reported that cigarette smoking, alcoholic beverage consumption, and inadequate consumption of fruits/vegetables were attributable risk factors for development of ESCC.[10] Moreover, some other known risk factors are oral snuff dipping and chewing betel quid, which are more commonly used in South and South-East Asian countries.[11] A meta-analysis of 16 studies reported that the intake of high-temperature food and beverages was associated with an increased rate of development of EC.[12]

Overall, socioeconomic status (SES) has been demonstrated to have effects on development of different types of cancer. Studies conducted in this regard have identified the risk of EC among people working in a manual trade, having lower than high school education, and among the low-income population.[13,14]

Despite improved surgical methods, decreased perioperative mortality, and the introduction of multimodal therapies, patients with EC demonstrated to have poor prognosis and fewer therapeutic effects. Most patients die within the first year of diagnosis and only 8–20% survive beyond five years. Accurate staging in such patients is essential because it guides and affects the treatment decision.[15,16] Diagnosis of EC requires a proper history, physical examination, and esophagoscopy, while the confirmation of the diagnosis requires a biopsy of the tumor for histopathological evaluation.[17]

Afghanistan being a country with limited resources, still has no large-scale published data to elaborate upon the risk factors associated with different cancers including EC. Only one published study so far has reviewed the association of diet with EC.[18] Thus, we conducted the current study and aimed to identify the risk factors related to the development of EC in Afghanistan.

Material and Methods

Design

This was an unmatched case-control study to explore the associated risk factors for EC.

Study Population and Setting

The study included 132 EC patients and 132 controls with a total of 264 participants, from January 1, 2019 to December 31, 2019. The endoscopic and excisional biopsies diagnosed as EC were collected in Department of Pathology and Clinical Laboratory of French Medical Institute for Mother and Children (FMIC) and in Ward of Clinical Oncology of Jamhoryat Tertiary Care Hospital (JTCH). The Department of Pathology and Clinical Laboratory of FMIC is the only well-equipped department in the country that provides standard histopathology services in Afghanistan. JTCH is a governmental hospital and the only hospital in Afghanistan that provides oncology services. Therefore, our study could include the entire country samples as most of the cases are referred to these two main hospitals. Cases were included with confirmed diagnosis of EC by histopathologic examination and whether the patients were willing to be part our study. The controls were selected from adult participants who were visiting the mentioned hospitals for routine health check-ups and whether they were willing to be part of our study. Patients with an active cancer or any signs of cancer, past history of cancer, and those who did not want to be part our study were excluded from the study. A structured self-evaluation questionnaire was used including direct interview of the participants who were willing to participate in our study, but were illiterate and could not complete the questionnaire. Only a few of the study

participants, who were educated, were given the questionnaire to fill by themselves. The questions were asked in both local languages (Pashto and Farsi) after informed consent was obtained from each participant.

Risk Factors

The questionnaire contained the following parameters: age, gender, and body mass index (BMI). BMI for both case and control groups was classified into four categories as suggested by the World Health Organization (WHO):[19] below 18.5 categorized as underweight, 18.5–24.9 as normal, 25–29.9 as overweight, and more than 30 as obese. Place of living according to country zones and urban vs rural area. Urban area is defined as the capital or central cities of the provinces while the districts and villages of the country were defined as rural area. Ethnicity was classified according to main available ethnicity groups in Afghanistan (Tajik, Pashtun, Hazara, Uzbek, or Turkmen). Education level was categorized as illiterate, school-level education, and university level or more. The economy status was categorized as low, middle, and high income based on their income from all available sources as low; just meet routine expenses, middle; meet the routine expenses and emergencies, and high: able to save or invest money. This type of categorization has been used in previous studies.[20] Physical exercise level was categorized as routinely exercise or no exercise. Participants were also asked about their occupations as housewife, farmer, unskilled labor worker, and professional/business work. The female patients in our study were categorized as housewives as the majority of women in Afghanistan are not allowed to work outside the confines of their houses. Cigarette smoking was categorized as smoker and nonsmoker and the response of subjects were recorded as "Yes" or "No". Meanwhile, the participants were asked for the duration in years and the number of cigarettes smoked per day. Considering the use of oral snuff, the responses for subjects who were using snuff or not were reported as "Yes" or "No", respectively. The available duration of oral snuff usage in our study recorded up to 20 years. In a previous study the oral snuff usage was categorized as 1–10 years, 11–20 years and more than 20 years,[21] therefore, we categorized as 1–10 years and more than 10 years. Similarly, alcohol drink was categorized as drinkers vs non-drinkers.

Consumption of green tea was categorized according to the consumed amount based on a cup of 250 mL, which is commonly used in Afghanistan for drinking tea and it was categorized as four cups per day or more. In addition, participants were asked about the habit of drinking tea at a higher temperature or not. Drinking tea at ≥65°C can act as carcinogen for people.[22] Therefore, we have checked the temperature of the tea in two times after pouring in cup[1] immediate pouring up to two minutes the temperature was 75°C to 65°C and[2] after two minutes which will be lower than 65°C. We asked our participants based on time of drinking tea after pouring in cup and participants who drink immediately and fast within two minutes was counted as hot tea drinker and participants who were waiting and were drinking slowly after two minutes were counted as warm tea drinkers. Participants were also asked if they ever had the habit (eating it with daily meal) of spicy food and pickling vegetable consumption. Fresh fruit consumption was categorized as consuming once or less per week, twice per week, and more than twice per week. History of EC in first-degree relatives were also asked and the responses were recorded as "Yes" or "No". Patients were asked about the cancer history of first-degree family members only, because most of the patients did not know about the cancer history of their second-degree relatives. Similarly, the cancer history was classified according to the relation of the participant with a family member who had cancer.

Histopathology

All the tissue biopsies were received in formalin. Grossly, they were small gray-white endoscopic biopsied specimens. From each biopsy a microscopic slide was made after the tissue processing and staining with hematoxylin and eosin (H&E) stain. The stained slides were reviewed under the microscope and the diagnosis with histologic subtypes was confirmed.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS), version 26 was used for analyzing the data. Mean and standard deviation was calculated for continuous variables (age, weight, and height), and frequency and proportion were calculated for categorical variables. A binary logistic regression test of univariate analysis was used to estimate the risk of hypothesized

risk factors for their unadjusted associations with EC. Significant variables (p-value <0.05) in univariate logistic regression were further analyzed in a multivariate logistic regression model to see independent associations with EC. For each factor, we calculated the odds ratio (OR) with consideration of 95% confidence interval (CI).

Results

Descriptive results

Among cases, the predominant EC type was ESCC (74%) and the remaining were EAC (26%). The majority of cases were males (69.4%) and cases were mostly in the age group of 55–64 years (mean age: 59.48±9.9 years), while controls were mostly in the age group of 45–54 years (mean age: 48.05±11.02 years).

At the time of diagnosis, 81.8% of cases and 26.5% of controls were uneducated, 83.3% of cases and 13.6% of controls belongs to low-income families and 92.4% of cases and 42.4% of controls were living in rural areas of the country. Only 6.1% of cases were office employed and the rest were farmers, housewives, and laborers, whereas in control group, 46.4% were office employees (Table 1).

Among case group, 18.2% were smokers, 41.7% were oral snuff users, and 98.5% were nondrinkers, whereas in control group, 8.3% were smokers, 12.1% were using oral snuff and 100% were nondrinkers (Table 2). A higher proportion of case group drank tea at high temperature (61.4%), while it was only 22% in control group. Ninety-five point five percent of the case group and 72.7% of control group were not doing physical exercise. Moreover, 68.2% of people in the case group were consuming fresh fruit only once a week or less, while in the control group 58.3% of people were consuming fresh fruit more than twice per week. Only 3% of people in case group consumed the fresh fruit more than twice per week (Table 3). Our findings also showed that 43.5% of people in the case group had family history of cancer, which was only 14.4% in the control group (Table 1).

Inferential results

For all the main variables, we run univariate conditional logistic regression analysis. The univariate analysis showed significant p-value for older ages, male gender, rural area residents, Pashtun ethnicity, low level of education, labor occupation, family history of cancer, cigarette smoking, use of oral snuff, drinking more than four cups of tea per day, hot tea consumption, less consumption of fresh fruit, and lack of exercise. The details have been shown in Tables 4 and 5. The variables that showed a significant OR in the univariate analysis were selected for multivariate conditional logistic regression analysis as the final model shown in Table 6. Based on statistical analysis in our final model, we found that the incidence of EC was higher in the older age group (OR: 1.108, 95%CI, p-value <0.001), and also males had a higher chance of developing EC (OR: 3.875, 95%CI, p-value=0.04). A greater risk of developing EC was found in uneducated individuals (OR: 13.945, 95%CI, p-value=0.042), compared to those who were educated at the school level or even higher. Residence in rural areas was presumed to be strongly associated with increased risk of developing EC (OR: 29.52, 95%CI, p-value <0.001). Subjects with habit of oral snuff dipping showed an increased risk of having EC in the multivariate regression model (OR: 4.541, 95%CI, p-value=0.043), while the duration of snuff dipping and ex-snuff users versus current users showed no significant difference.

In our study we did not find any statistically significant association between smoking cigarettes and alcohol consumption with an increased risk of EC.

Consumption of hot tea was significantly associated with the development of EC by more than fivefold (OR: 5.395, 95%CI, p-value=0.004), whereas the amount of tea consumed did not have an impact on EC risk. In addition, BMI, consumption of spicy food and pickled vegetable showed no significant association with EC.

An elevated risk of developing EC was noted amongst subjects consuming fresh fruits once a week or less compared to those subjects who consumed it more than twice a week (OR: 93.18, 95%CI, p-value <0.001). Overall lack of exercise was also associated with increased risk of developing EC (OR: 32.54, 95%CI, p-value=0.001). Although, the vast majority of the case-subjects were in the low-income category (83.3%) compared to 13.6% of participants in the control group who had low income, still there was no statistically significant association between low income and development

Table 1 Sociodemography and Family History of the Study Populations

Variables	Subgroups	Controls	Cases
		n (%)	n (%)
Age group (years)	25–34	10 (7.6)	0 (0)
	35–44	43 (33)	9 (6.8)
	45–54	45 (34)	27 (20.5)
	55–64	20 (15)	52 (40.2)
	≥65	14 (11)	44 (33.3)
Age range (years)		28–90	35–85
Mean age (years) ±SD		48.05±11.02	59.48±9.9
Gender	Male	52 (39.4)	92 (69.7)
	Female	80 (60.6)	40 (30.3)
BMI	Underweight	2 (1.5)	5 (3.8)
	Normal	85 (64.4)	92 (69.7)
	Overweight	35 (26.5)	30 (22.7)
	Obese	10 (7.6)	5 (3.8)
Ethnicity group	Tajik	58 (43.9)	41 (28.1)
	Pashtun	37 (28)	42 (31.8)
	Hazara	28 (21.2)	25 (18.9)
	Uzbek-Turkmen	7 (5.3)	21 (15.9)
	Others	2 (1.5)	3 (2.3)
Education level	Illiterate	35 (26.5)	108 (81.8)
	School-level	50 (37.9)	21 (15.9)
	University or more	47 (35.6)	3 (2.3)
Residence	Rural	56 (42.4)	122 (92.4)
	Urban	76 (57.6)	10 (7.6)
Country zone	Center	64 (48.5)	49 (37.4)
	North-East	15 (11.4)	28 (21.2)
	North	12 (9.8)	20 (15.2)
	West	13 (9.1)	8 (6.1)
	South	5 (3.8)	4 (3.1)
	South-East	15 (11.4)	18 (13.7)
	East	8 (6.1)	5 (3.8)
Occupation	Farmer	4 (3)	66 (50)
	Housewife	49 (37.1)	37 (28)
	Labors	20 (15.2)	21 (15.9)
	Professional/business	59 (44.7)	8 (6.1)
Income	Low	18 (13.6)	110 (83.3)
	Middle	93 (70.5)	22 (%16.7)
	High	21 (15.9)	0 (0)
Exercise	Never	96 (72.7)	126 (95.5)
	Ever	36 (27.3)	6 (4.5)
Family history of cancer	No	113 (85.6)	74 (56.5)
	Yes	19 (14.4)	57 (43.5)
Family history relationship	Parents	13 (72.2)	15 (48.4)
	Brothers/sisters	5 (27.8)	16 (56.6)

Abbreviations: SD, standard deviation; BMI, body mass index.

Table 2 Hazardous Habits of the Study Participants

Variables	Subgroups	Controls	Cases
		n (%)	n (%)
Smoking	Never smoking Ever smoking	121 (91.7) 11 (8.3)	108 (81.8) 24 (18.2)
Smoking duration	Up to 10 years 10–20 years >20 years	7 (63.6) 3 (27.3) 1 (9.1)	7 (29.2) 10 (41.7) 7 (29.2)
Number of smoking	Up to 10 cigarettes/day 10–20 cigarettes/day >20 cigarettes/day	7 (70) 3 (30) 0 (0)	5 (22.7) 11 (50) 6 (27.3)
Snuff habit	Never Ever user	116 (87.9) 16 (12.1)	77 (58.3) 55 (41.7)
Snuff using duration	Up to 10 years >10 years	6 (37.5) 10 (62.5)	6 (11.8) 45 (88.2)
Alcohol consumption	No Yes	132 (100) 0 (0)	130 (98.5) 2 (1.5)

Table 3 Dietary Characteristics of the Study Participants

Variables	Subgroups	Controls	Cases
		n (%)	n (%)
Tea drinking habit	Up to 4 cups/day >4 cups/day	33 (25) 99 (75)	20 (15.1) 112 (84.8)
Hot tea habit	No Yes	103 (78) 29 (22)	51 (38.6) 81 (61.4)
Spicy food habit	No Yes	80 (59.8) 52 (39.2)	86 (65.2) 10 (7.6)
Pickled vegetable habit	No Yes	81 (61.4) 51 (38.6)	88 (66.7) 44 (33.3)
Fresh fruit consumption	Once/week Twice/week >Twice a week	20 (15.2) 35 (26.5) 77 (58.3)	90 (68.2) 38 (28.8) 4 (3)

of EC, in the final logistic regression model. In addition, there was no association of development of EC with their occupation.

Finally, the study demonstrated that having of EC in first-degree relatives increased the risk of EC by 14-fold compared to those who did not have a family history of EC (OR: 14.50, 95%CI, p-value=0.003).

Discussion

Environmental and geographical factors have a strong association with the development of EC, compared to other cancers. The risk of EC rises with age; studies in India, Tanzania, and China have reported that the majority of EC cases occurred in the age group of >60, >65, and 60–69 years, respectively.[23–25] Consistent with these results, our study also demonstrated that many EC cases were in the age group between 55 and 64 years (mean age: 59.4 years) at diagnosis.

Table 4 Univariate Conditional Logistic Regression Analysis of Sociodemographic and Family History

Characteristics	Subgroups	OR	95%CI		*p*-value
Age		1.103	1.073	1.134	<0.001
Gender	Male	3.538	2.12	5.89	<0.001
	Female	1			
BMI	Normal	1			0.326
	Underweight	2.3	0.436	12.22	
	Overweight	0.792	0.448	1.4	
	Obese	0.462	1.52	1.406	
Country zone	Central zone	1			0.196
	North-East zone	0.022	1.13	4.892	
	North zone	0.084	0.911	4.433	
	West zone	0.779	0.33	2.294	
	South Zone	0.95	0.266	4.097	
	South-East zone	0.259	0.719	3.418	
	East zone	0.736	0.251	2.65	
Residence	Rural	16.557	7.969	34.402	<0.001
	Urban	1			
Ethnicity	Pashtun	1			0.021
	Tajik	0.615	0.342	1.106	
	Hazara	0.771	0.386	1.541	
	Uzbek	2.591	0.993	6.761	
Education level	Illiterate	45.907	13.589	155.091	<0.001
	School-level education	1.119	0.214	5.847	
	Higher educations	1			
Income	Low	9.9	0	0	0.998
	Middle	3.8	0	0	0.998
	High	1			
Occupations	Farmer	121.687	34.845	424.962	<0.001
	Housewife	5.569	2.373	13.068	<0.001
	Labors	7.744	2.967	20.211	<0.001
	Professional/business	1			
Family history of cancer	No	1			
	Yes	4.581	2.524	8.316	<0.001

Abbreviation: BMI, body mass index.

In the current study, a large proportion of EC cases were constituted by males. The sex distribution was similar to those studies reported in Tanzania,[24] the USA,[26] the UK,[27] and GLOBOCAN project reports of EC for Asian countries.[28] The probable reason for higher EC in men could be related to higher exposure of various environmental factors such as farming, smoking, alcohol consumption, and snuff dipping, which are common among males, especially in low-income countries like Afghanistan.

Our results indicated that the risk of EC was significantly high among uneducated individuals and rural area residents. Similar findings were reported in studies conducted in India[29,30] and Turkey, which demonstrated a significant high risk of EC among rural area residents.[31] Increased risk of EC amongt individuals with low education and low SES was unexpectedly reported in developed countries as well, such as USA[13] and Sweden.[14]

Table 5 Univariate Conditional Logistic Regression Analysis of Hazardous Habits Eating Habits and Physical Exercise

Variables	Subgroups	OR	95%CI		*p*-value
Smoking	No smoking Smoker	1 2.444	1.144	5.223	0.021
Number of smoking	Up to 10 cigarettes/day >10 cigarettes/day	1 7.933	1.478	42.581	0.016
Oral snuff	No habit Habit of the snuff	1 5.179	2.767	9.693	<0.001
Snuff using status	Current user Ex-user	14.333	3.752	54.761	<0.001
Snuff duration	Up to 10 years >10 years	1 4.5	1.199	16.894	0.026
Tea drinking	Up to 4 cups/day >4 cups/day	1 1.867	1.006	3.462	0.048
Hot tea	No Yes	1 5.641	3.285	9.688	<0.001
Spicy food	No Yes	1 0.823	0.499	1.357	0.445
Pickled food	No Yes	1 0.794	0.48	1.314	0.37
Fresh fruit consumption	Once/week Twice/week >Twice/week	86.625 20.9 1	28.383 6.922	264.38 63.104	<0.001 <0.001
Physical exercise	Never Yes	9.8 1	3.996	24.035	<0.001

Our results revealed no statistically significant relationship between low income and EC, although 83% of EC patients in our study belonged to low income and none of them belong to high income. Despite the fact that being unemployed and working as farmer have been reported as risk factors for developing EC in previous studies,[32,33] the majority of EC patients in our study were unemployed (93.9%), of whom 75% were farmers and all the female cases were housewives, but statistically significant correlation was not found. The work environment in agriculture is complex, with many potential hazardous exposures, such as pesticides, herbicides, fertilizers, dust, zoonotic microbes, and sunlight with high potential to cause EC.[34]

In current study, we observed a 4.5-times higher risk of EC among oral snuff users. These findings were in line with the results of a study conducted in three health centers including Kuwait, Pakistan, and UK, and another study in Sweden.[35] On the contrary, other studies showed no correlation between development of EC and oral snuffing.[36,37] Such conflicting results may be due to different compositions and methods used for preparing oral snuffs. Unexpectedly, cigarette smoking and alcohol consumption showed no significant association with EC in our study, whereas both have been reported as risk factors for EC in the majority of studies conducted in Western and Asian countries.[38] However, there are studies which illustrated that smoking and alcohol consumption were less significant risk factors for EC in high incidence areas of EC, such as in Central Asia, known as central Asian esophageal cancer belt.[39] Studies conducted in Iran[40] and China[41] also demonstrated that alcohol consumption was not the main risk factor for EC.

Table 6 Multivariate Conditional Logistic Regression Analysis of Risk Factors

Characteristics	Subgroups	OR	95%CI		*p*-value
Age		1.115	1.048	1.186	0.001
Gender	Male Female	4.628 1	4.907	19.966	0.026
Education level	Illiterate School-level Higher educations	13.945 0.355 1	1.105 0.009	175.933 14.526	0.042 0.585
Living area	Rural Urban	46.645 1	7.932	274.29	<0.001
Oral snuff using	No Yes	1 6.105	1.207	30.889	0.029
Hot tea	No Yes	1 5.719	1.681	19.45	0.005
Fruit consumption	Once or less/week Twice/week >Twice/week	93.186 20.637 1	10.403 2.697	834.738 157.894	<0.001 0.004
Exercise	No Yes	32.548 1	4.145	255.555	0.001
Family history of cancer	No Yes	1 14.506	2.46	85.545	0.003

Our study suggested that hot tea drinkers were at a 5.7-fold increased risk of EC compared to those who did not drink hot tea. Previous studies showed that drinking tea at a high temperature compared with drinking warm tea was highly associated with the risk of EC.[42,43] The role of hot tea in association with EC has been previously suggested in 1930[44] and the carcinogenesis may be related to chronic thermal damage to the esophageal mucosa. The IARC has recently listed drinking scalding hot beverages (>65°C) as likely to be carcinogenic for humans.[22]

A study reported spicy food and pickled vegetables as risk factors for gastrointestinal (GI) tumors.[45] In a meta-analysis that included 39 articles related to intake of spicy food and cancer risk, 30 studies showed a positive association, and nine articles showed no association.[46] In contrast, the findings of our study showed no significant relation between EC and eating spicy foods or pickled vegetables.

The protective effects of consumption of fresh fruits against the development of GI tract carcinomas has already been reported;[47] a study reported an 11% decreased risk of EC with an intake of 100 gr of fresh fruit per day.[48] Our study concluded an increased risk of EC among individuals eating fresh fruit less than once, once, or up to twice per week than those who ate fresh fruits more than twice per week. Most fresh vegetables and fruits contain high levels of potentially protective compounds and anticarcinogenic substances, such as fiber, antioxidant vitamins, minerals, dithiolthiones, isothiocyanates, indole-3-carbinols, flavonols, and lignans.[49] Citrus fruits have a lot of vitamin C, antioxidants, and antimutagenic compounds which cause tumor growth suppressors and apoptosis.[50]

Physical exercise is another protective factor against cancers that has been previously reported.[51] The current study also reinforced the relationship between EC and physical exercise. The exact mechanism of exercise and its protection against cancer is not yet elucidated, but the hypothesized mechanisms include changes in the growth factor levels of endogenous sexual and metabolic hormones, reduced obesity, in particular, the central adiposity, and probable positive changes in the immune system functions.[52]

In addition to environmental risk factors, hereditary susceptibility was another noticeable risk factor for EC.[53] Chen et al[54] reported positive family history had a twofold increase in risk for developing EC and an eightfold risk for those

whose both parents had cancer. The present study also revealed that the family history of EC in first-degree relatives increased the risk of EC. A multicenter case-control study in the USA revealed no statistically significant risk of positive family history with EC.[55] The inconsistency in the results from different studies might be due to different genetic susceptibility profiles and the differences in the triggering environmental risk factors.

This is the first case-control study conducted in Afghanistan considering a wide range of associated risk factors for EC. The study had been conducted in two main pathology and oncology centers that receives patients and biopsy samples from all around the country and all EC cases were diagnosed by standard histopathologic examinations. Due to limited availability of diagnostic pathology centers in Afghanistan, we included a relatively smaller number of cases in our study. Also, the risk factors in our study were not evaluated in vivid detail. Lastly, it was unmatched sample collection, so there might be some unbalanced factors between various groups that were undetectable.

Conclusion

There is a growing occurrence of EC in Afghanistan, but very limited data are available about various determinants and risk factors. Our study concluded that EC was a common cancer in older age groups (>65 years) and male gender. Our study also provided evidence that living in rural areas, being uneducated, using oral snuff, drinking hot tea, less consumption of fresh fruit/ vegetables, having less physical exercise, and having a family history of cancer were possible contributors to the development of EC. These positive associations can help to suggest EC preventive measures and screening programs, leading to early detection of EC in people who have more exposure to the abovementioned risk factors.

Abbreviations

EC, esophageal carcinoma; ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; FMIC, French Medical Institute for Mothers and Children; SPSS, Statistical Package for Social Sciences; SES, socioeconomic status; IARC, International Agency for Research on Cancer; UK, United Kingdom; USA, United States of America; GI, gastrointestinal.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

The project was approved by the Ethical Review Committee of FMIC (37-FMIC-ER-18).

Consent for Publication

Before participation, each participant autonomously chose to accept or reject to be part of this research and detailed information about the study was provided to each participant as well. An informed consent form developed in local languages and translated to English was obtained from each participant. We certify that all participants gave informed consent and that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

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Disclosure

The authors report no conflicts of interest in this work.

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