

## Original Article

## Prevalence of Esophageal Cancer Risk Factors among Turkmen and Non-Turkmen Ethnic Groups in a High Incidence Area in Iran

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**Background:** Golestan Province in north-eastern Iran has one of the highest incidence rates for esophageal squamous cell carcinoma (ESCC) worldwide. Earlier studies have reported higher incidence rates in the areas of Golestan which are mainly inhabited by individuals of the Turkmen ethnic group. However, it is not clear whether in those areas the incidence among Turkmens is higher in comparison to non-Turkmens. Some previous studies have suggested that environmental factors might play a more essential role in ESCC carcinogenesis in Golestan than a genetic background. If environmental factors instead of a genetic background are the major risk factors, therefore the prevalence of known environmental risk factors would not significantly differ among ESCC cases of different ethnic groups. To investigate the role of environmental factors versus genetic background by using the above concept, we have compared the prevalence of known risk factors for ESCC among Turkmen and non-Turkmen ESCC cases.

**Methods:** Study participants were histopathologically proven ESCC cases from Golestan Province. They were recruited in the study from December 2003 to June 2007. The prevalence of the most important known risk factors for ESCC in Turkmen and non-Turkmen ESCC cases was compared using Chi-squared and Fisher's exact tests.

**Results:** Of 300 ESCC cases recruited in the study, 171 (57.0%) and 129 (43.0%) cases were Turkmen and non-Turkmen, respectively. In the majority of the investigated risk factors which included tobacco, nass, and opium use, hot and extremely hot tea consumption, as well as decreased levels of education; there was no significant difference between Turkmen and non-Turkmen ESCC cases in the prevalence of exposure.

**Conclusion:** Our findings support the suggestion that a substantial difference between Turkmens and non-Turkmens in terms of genetic susceptibility to ESCC is unlikely. Nevertheless, the moderate effect of genetic factors cannot be ruled out. Further studies to investigate potential environmental and genetic risk factors of ESCC in Golestan and the interaction between environmental and genetic factors are warranted.

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**Keywords:** Esophageal squamous cell carcinoma (ESCC) • ethnicity • North-East Iran

### Introduction

Esophageal cancer is among the ten most prevalent malignancies and is the sixth leading cause of cancer deaths worldwide.<sup>1</sup> Squamous cell carcinoma is the most common type of esophageal tumor. The incidence of this cancer type has a high geographical variation and the difference may be as high as 50-fold in some regions of the world.<sup>2</sup> Very high incidence rates for esophageal squamous cell carcinoma (ESCC) have been reported from certain

areas of the world, including the northern areas of China and Golestan Province in north-eastern

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Iran.<sup>3-5</sup> Approximately half of the inhabitants who reside in the high incidence areas of Golestan Province are from the Turkmen ethnic group; the other half consists of individuals from other ethnic groups, including Persian, Turk, Kurd, Sistani and Baloochi. It has been suggested that ESCC might be more common in Turkmens than in individuals from other ethnic groups.<sup>4-6</sup> However, this suggestion has yet to be evaluated in incidence studies. A study on the familial risks of esophageal cancer among Turkmens in Golestan has suggested an inheritable pattern for ESCC among the Turkmen population. An earlier study also reported a noticeable positive family history of esophageal cancer for Turkmen ESCC patients.<sup>4,7</sup> On the other hand, no significant difference in the prevalence or pattern of p53 mutations has been found in a recent study between esophageal cancer patients from northern Iran and Tehran, the capital of Iran, which is a low- to moderate-risk area for ESCC.<sup>8</sup> This finding, as well as the reported decline in ESCC incidence in Golestan during the past few decades, may be related to an improvement in socioeconomic conditions in the province<sup>9</sup> which suggests that environmental factors may have a more prominent role than genetic background in ESCC carcinogenesis in north-eastern Iran.

The environmental risk factors that have shown an association with ESCC risk in Golestan are cigarette smoking, nass chewing, opium use, hot tea consumption, certain nutritional deficiencies, poor oral hygiene, and low socioeconomic status.<sup>10</sup> Other suggested risk factors are exposure to polycyclic aromatic hydrocarbons (PAHs), nitrosamines, silica fibers, and infectious agents.<sup>11</sup> PAHs are produced by the incomplete combustion of organic materials.<sup>12</sup> Additionally, a study on the food and urine samples in high risk areas for ESCC has revealed high levels of PAH exposure amongst individuals who reside there.<sup>13-15</sup>

As discussed above, in the high-incidence areas of Golestan it is still not clear whether the incidence of ESCC among Turkmens is higher than non-Turkmens. If we assume that environmental factors are major risk factors for ESCC carcinogenesis in Golestan, therefore the prevalence of risk factors would not differ significantly among ESCC cases from different ethnic groups. On the other hand, if genetic background has a prominent impact on ESCC development, we would expect a higher prevalence of environmental risk factors among individuals that are not genetically susceptible in comparison

to susceptible individuals. In the current study to investigate this hypothesis, we have compared the prevalence of known risk factors for ESCC in Golestan, including tobacco and opium use, hot tea consumption, and decreased level of education, among ESCC cases from the Turkmen and non-Turkmen ethnic groups. Although education level is not a direct etiologic factor, it is an indicator for socioeconomic status and can be considered as a proxy for several more direct environmental risk factors.

## Patients and Methods

The case subjects included all patients that were referred to Atrak Clinic from December 2003 to June 2007 who received a histopathological diagnosis of ESCC and agreed to participate in the study. Atrak Clinic is the only specialized clinic for upper gastrointestinal tract cancers located in the high-incidence areas of Golestan and is established and affiliated with the Digestive Disease Research Center (DDRC) of Tehran University of Medical Sciences. For the cases that agreed to participate the inclusion criteria included: at least 18 years of age, residing in Golestan at the time of enrollment, and no history of any other malignancy. Results of the Golestan Cancer Registry show that approximately 70% of all incident cases in this area during this time period were in fact referred to Atrak Clinic (unpublished data). The study was reviewed and approved by the Institutional Review Board of the DDRC.

After obtaining written informed consents, participants were interviewed by trained interviewers who collected detailed information on demographic characteristics, history of tobacco, opium, and alcohol use, highest education level attained, and tea drinking temperature with the use of a structured questionnaire.

## Statistical analysis

Mean age (and standard deviation) was calculated for Turkmen and non-Turkmen ESCC cases and the *P* value for difference was calculated using *t*-tests. The prevalence of known risk factors in ESCC cases from Turkmen and non-Turkmen ethnic groups was compared using chi-square tests and, if necessary, Fisher's exact tests. Alcohol use among study participants was negligible and therefore was not included in the analysis. We calculated cumulative use for cigarette smoking, nass chewing, and opium use by multiplying the

intensity of daily use by duration of use (years). The cumulative use variables were categorized into three groups: never used, cumulative use  $\leq$  the median, and cumulative use above the median. Since there was a highly significant difference between cases and controls regarding place of residence (rural vs. urban), we stratified our analyses by rural/urban status. Two sided  $P$  values below 0.05 were considered as statistically significant. SPSS version 15 was used for all statistical analyses.

## Results

A total of 300 ESCC cases were recruited in the study, of which 171 (57.0%) and 129 (43.0%) cases were Turkmen and non-Turkmen, respectively. The distribution of demographic variables in Turkmen and non-Turkmen cases is presented in Table 1. The mean age (SD) in Turkmen and non-Turkmen cases was 63.5 (10.8) and 65.4 (10.5) years, respectively. There was no significant difference between the two groups in mean age ( $P=0.16$ ). There was a difference in gender composition of recruited Turkmen and non-Turkmen ESCC cases; statistically, the difference was marginally significant ( $P=0.05$ ). The difference between the two groups regarding place of residence was highly significant ( $P<0.001$ ). While 58% of non-Turkmen cases came from urban areas, 83% of Turkmen cases resided in rural areas.

In analyses stratified by place of residence, there was no significant difference between Turkmen and non-Turkmen ESCC cases in the majority of the investigated factors, including tobacco and opium use, nass and opium cumulative use, hot and extremely hot tea consumption, as well as education level (Table 2). The sole significant difference was observed for cumulative cigarette smoking in rural areas; the cumulative use was higher among Turkmen than non-Turkmen ( $P<0.001$ ). No significant difference was observed for cumulative cigarette use in the

urban areas ( $P<0.001$ ). As expected, more urban than rural cases had some formal education (22.0 – 25.0% vs. 4.0 – 8%), but there was no significant difference between Turkmen and non-Turkmen in both rural and urban areas. Likewise, there was no difference between the two groups in terms of gender (data not shown).

## Discussion

Many environmental and genetic factors are presumed to be involved in the carcinogenesis of ESCC.<sup>11</sup> Lifestyle and personal habits are widely variable among human communities and ethnicities, therefore genetic factors can change populations' vulnerabilities to endogenous and exogenous carcinogenic factors.<sup>16,17</sup> Environmental carcinogens can invade the genetic material of the cell and make irreversible changes as hazardous and cancer triggering mutations.<sup>18,19</sup> Interactions between environmental and genetic factors have been suggested in the development of certain cancers. By those interactions, genetically susceptible people would be at higher risk than less-susceptible persons when exposed to moderate intensities of environmental risk factors.

If we assume that ESCC is more common among Turkmen than non-Turkmen in Golestan, we expect that the development of ESCC would be more likely in susceptible Turkmen than non-Turkmen when exposed to certain levels of environmental risk factors. In other words, to develop ESCC, the prevalence or intensity of exposure for non-Turkmen should be higher than for Turkmen. When we compared known risk habits, including cigarette, nass, and opium use, drinking hot tea, and education (as an indicator for SES) in Turkmen and non-Turkmen ESCC cases; we found no significant difference in the prevalence or intensity of exposure, with the exception of cumulative cigarette use in rural areas, which was also significantly higher amongst Turkmen. These findings suggest that higher susceptibility of Turkmen in Golestan to ESCC,

**Table 1.** Characteristics of study participants (ESCC cases)

	Turkmen	Non-Turkmen	P-value
Age [mean (SD), year]	63.7 (11.3)	65.5 (11.0)	0.16
Gender			
Male	94 (55.0%)	56 (43.4%)	0.05
Female	77 (45.0%)	73 (56.6%)	
Place of residence			
Rural	143 (83.3%)	75 (58.1%)	< 0.001
Urban	28 (16.4%)	54 (41.9%)	

SD= standard deviation

**Table 2.** Frequency (%) of cigarette smoking among Turkmen and non-Turkmen esophageal cancer cases

Ethnicity	Rural			Urban		
	Turkmen	Non-Turkmen	P-value	Turkmen	Non-Turkmen	P-value
Tobacco use *			0.78			0.85
Never-used	98 (68.5%)	50 (66.7%)		17 (60.7%)	31 (58.5%)	
Reported use	45 (31.5%)	25 (33.3%)		11 (39.3%)	22 (41.5%)	
Cigarette cumulative smoking <sup>+</sup>			0.01 †			0.21 †
Never-used	106 (74.1%)	69 (92.0%)		20 (71.4%)	37 (69.8%)	
≤ median (13.5 pack-years)	19 (13.3%)	3 (4.0%)		1 (3.6%)	8 (15.1%)	
> median	18 (12.6%)	3 (4.0%)		7 (25.0%)	8 (15.1%)	
Nass cumulative use <sup>+</sup>			0.28 †			0.19 †
Never-used	123 (86.0%)	65 (86.7%)		21 (75.0%)	47 (87.0%)	
≤ median (150 nass-years)	6 (4.2%)	7 (9.3%)		5 (17.9%)	4 (7.4%)	
> median	14 (9.8%)	3 (4.0%)		2 (7.1%)	3 (5.6%)	
Opium use			0.21			0.14
Never-used	97 (67.8%)	57 (76.0%)		22 (78.6%)	33 (62.6%)	
Reported use	46 (32.2%)	18 (24.0%)		6 (21.4%)	20 (37.7%)	
Opium cumulative use <sup>+</sup>			0.28			0.19
Never-used	101 (70.6%)	60 (80.0%)		23 (82.1%)	43 (79.6%)	
≤ median (15.5 unit-years)	21 (14.7%)	6 (8.0%)		0 (0.0%)	5 (9.3%)	
> median	21 (14.7%)	9 (12.0%)		5 (17.9%)	6 (11.1%)	
Drinking tea temperature			0.65			0.66 †
Cold/lukewarm	66 (46.5%)	31 (41.3%)		12 (42.9%)	18 (34.0%)	
Hot	49 (34.5%)	26 (34.7%)		11 (39.3%)	22 (41.5%)	
Very hot	27 (19.0%)	18 (24.0%)		5 (17.9%)	13 (24.5%)	
Education level			0.39 †			0.78
No school	132 (92.3%)	72 (96.0%)		21 (75.0%)	42 (77.8%)	
Some school	11 (7.7%)	3 (4.0%)		7 (25.0%)	12 (22.2%)	

\* Including tobacco smoking and nass chewing; <sup>+</sup> Cumulative use was calculated by multiplying intensity of use (per day) by duration of use (in years); † P-value calculated using Fisher's exact test

when compared to non-Turkmens, is unlikely.

All the investigated factors are known risk factors for ESCC in Golestan. Cigarette smoking, nass chewing and opium use all have significant associations with ESCC risk in Golestan.<sup>20</sup> Nass consumption is frequently seen among Turkmens, particularly in rural regions and in early studies has been mentioned as a potential risk factor. In the present study, however, the results do not support previous reports.<sup>4,5,21</sup> Extracts of a certain type of opium from Golestan have also shown mutagenic activities *in vitro*<sup>22</sup> and has been considered as a risk factor for ESCC but our results and another report have shown no difference amongst Turkmens and non-Turkmens.<sup>20</sup> Hot tea consumption, which is a very common habit in Golestan, is one of the strongest environmental risk factors for ESCC in that region.<sup>23,24</sup> Poor socio-economic status, including low education level, is also significantly associated with ESCC risk.<sup>25,26</sup>

Although our findings suggest the lack of a large difference between Turkmens and non-Turkmens in ESCC susceptibility, and environmental factors are the main risk factors for

ESCC in Golestan, we cannot exclude moderate interactions between genetic and environmental factors in certain individuals, regardless of their ethnical background. Further studies are warranted to investigate these interactions. Some risk factors are shown to be more common in rural areas than in urban areas of Golestan and the longer duration of residence in rural areas has shown a significant association with ESCC risk.<sup>25</sup> The previously suggested higher incidence of ESCC among Turkmens may be related to the fact that, in the high incidence areas of Golestan, more Turkmens than non-Turkmens may live in rural areas. Cancer registration studies in Golestan with stratifications for ethnic groups and residential areas will be helpful to investigate this issue.

Overall, we found no significant difference in the prevalence of risk factors among ESCC cases from different ethnic groups in Golestan. This supports the idea that any large difference between Turkmens and non-Turkmens in genetic susceptibility to ESCC is unlikely. Nevertheless, a moderate effect of genetic factors cannot be excluded. Further studies to investigate potential

environmental and genetic risk factors of ESCC in Golestan and interactions between environmental and genetic factors are warranted.

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