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Familial risks of esophageal cancer among the Turkmen population of the Caspian littoral of Iran

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Abstract

In northeastern Iran, there is an area of high incidence of esophageal cancer, which is populated by residents of Turkmen ancestry. Several environmental risk factors for esophageal cancer have been proposed, but the roles of familial and genetic factors have not been studied extensively in the Turkmen population. We evaluated the importance of familial risk factors for esophageal cancer by performing a case-control study of 167 cases of esophageal squamous cell carcinoma and 200 controls of Turkmen ethnicity. Detailed family pedigrees of the cases and controls were constructed, which documented all cancers in first- and second-degree relatives. The actuarial risk of cancer was then estimated in 2,097 first-degree relatives of cases and 2,783 first-degree relatives of the controls. A hazard ratio was constructed, based on a comparison of the 2 cumulative incidence curves. The risk to age 75 of esophageal cancer in the first-degree relatives of Turkmen patients with esophageal cancer was 34% *versus* 14% for the first-degree relatives of the controls (hazard ratio = 2.3; $p = 3 \times 10^{-8}$). Cases (9.6%) reported that their parents were related, *versus* 2.5% of the controls who reported this. (odds ratio = 4.1; *p* value = 0.006). Familial factors are important in the etiology of esophageal cancer among the Turkmen residents of Iran. The hazard ratio of 2.3 for cancer among first-degree relatives is consistent with an important contribution of heritable factors. It will be of interest to perform marker studies to establish which genes are responsible. © 2006 Wiley-Liss, Inc.

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Article Text

Esophageal cancer is among the 10 most common malignancies worldwide, and ranks as the 6th leading cause of death from cancer.[1] It constitutes 7% of all gastrointestinal (GI) cancers and is one of the most lethal of all cancers.[2][3] The incidence of esophageal cancer varies greatly between populations, with a greater than 50-fold difference observed between rates in high- and low-risk populations.[3] It is much more common in Asia than in western countries. The esophageal cancer belt is a geographic area of high incidence, which stretches from north-central China westward through Central Asia to northern Iran.[4][5] In Linxian, north of China, the annual incidence rate of esophageal cancer was 151/100,000 for males and 115/100,000 for females in the 1970s.[6] Farther west, in Gonbad, northeastern Iran, the annual incidence rate was reported to be 109/100,000 per year for men and 174/100,000 per year for women.[7][8] It seems that the incidence of esophageal cancer in Turkmen ethnicity is more than that in other inhabitants of this area.[7][8][9] The incidence rates in China and Iran appear to have decreased during the last 3 decades, but are still ~100/100,000 per year for both males and females in these high incidence areas.[6][9][10]

Gonbad is the second largest city of Golestan province in Iran and is located in the eastern semi-desert plain of the province. It is mainly populated by people of Turkmen ethnicity, who descended from the Oguz Turkic tribes who migrated from the Altai Mountains (on the border of China and Mongolia) to northern Iran.[11] Turkmen have oriental facial features and are believed to have a genetic background similar to that of East Asians.

There are 2 main forms of esophageal cancer: squamous cell carcinoma and adenocarcinoma. More than 90% of all esophageal cancer cases in Iran are of the squamous cell type.[10] The principle risk factors for esophageal cancer are thought to be environmental. Two of the known risk factors are tobacco smoking and alcohol consumption.[2][3][12] However, alcohol is rarely consumed by men in Northeastern Iran, and neither risk factor is common among women. In this area in Iran, proposed risk factors include a dietary deficiency of fruits and vegetables,[13] the consumption of very hot beverages[13][14] and exposure to carcinogens due to opium consumption.[15][16][17] However, neither the relative risks associated with these factors nor their prevalence in the Iranian population are of sufficient magnitude to explain the extremely high incidence. It is therefore important that familial factors also be explored as possible risk factors contributing to the development of squamous cell carcinoma of the esophagus in northeastern Iran. A central role for familial factors was suggested by the early observation of a family with 13 cases of esophageal cancer in a single village.[18] In a subsequent epidemiological study, Ghadirian et al. reported a positive family history of esophageal cancer in 47% of Turkmen patients with this disease.[19] The present study was undertaken to evaluate the existence of familial aggregation among esophageal cancer cases in northeastern of Iran and to quantify the risk associated with having an affected first-degree relative.

Material and methods

The city of Gonbad, the second major city of Golestan province, is located in the steppe grasslands of the Turkmen plain, in the easternmost district of the Caspian littoral in northeastern Iran. In August 2001, the Digestive Disease Research Center (DDRC) of Tehran University of Medical Sciences opened a referral clinic for upper GI tract cancers (the Atrak Clinic), where we presently

conduct a case-control study of upper GI malignancies. The clinic is located in Gonbad, at the largest hospital of eastern Golestan (the Khatam Hospital). The majority of cancer patients in this area first present to one of the local general practitioners, internists or surgeons. Only a small number of patients are first diagnosed in cities outside of this area. More than 70% of the patients in the city and the surrounding rural area are referred to the Atrak Clinic in Khatam Hospital for the investigation of upper GI disorders.

Cases

All patients who were referred to the Atrak Clinic between August 1, 2001 and April 15, 2005 for suspicion of having an upper GI cancer were eligible for study. After signing an informed consent, the patient was interviewed by a physician, using a structured questionnaire and the patient underwent a physical examination followed by an esophago-gastro-duodenal video endoscopy. Endoscopy was performed using a Pentax EPK-700 or Olympus CV-230 video endoscope. At least 4 punch biopsies were obtained from the suspected tumors' site. Biopsy specimens were oriented and spread on strips of filter paper and fixed immediately in 10% buffered formalin. The samples were sent to the DDRC in Tehran, where they were embedded, sectioned and stained with hematoxylin and eosin and examined by an experienced DDRC pathologist. Between August 1, 2001 and April 15, 2005, a total of 1,350 patients were referred to Atrak Clinic; of these, 358 patients were diagnosed with squamous cell carcinoma of the esophagus. One hundred and eighty were of Turkmen ethnicity and these are the subjects of present study. Thirteen patients were unable or were unwilling to provide pedigree data and were excluded, leaving 167 case subjects.

Controls

The control group consisted of 83 patients who were referred to the Atrak outpatient clinic between August 1, 2001 and April 15, 2005 for endoscopy but were found not to have esophageal (or any form of) cancer (Atrak Clinic controls). The diagnoses in the Atrak Clinic controls included gastroesophageal reflux disease, irritable bowel syndrome and acid peptic disease. In addition, we included as controls 137 inpatients of the Khatem Hospital who were diagnosed with a medical condition other than cancer (hospital controls). Controls were selected by one of us during a monthly visit to hospital inpatients. The diagnoses in hospital controls were nonmalignant gynecological diseases, trauma, hernia, cataract, gallstones, kidney stones, benign prostatic hypertrophy and hemorrhoids. In total, there were 220 controls, all of whom were Turkmen and aged 45 and above.

Pedigree data collection

Pedigrees were obtained from cases and controls between September 1, 2004 and May 1, 2005. A face-to-face interview was performed using a structured questionnaire in the home of the subjects. The research team consisted of a trained physician and a nurse who were familiar with pedigree construction. If the proband was alive and was in good health, he was interviewed. If the patient or the control had died (96 cases, 16 controls), or was in a poor health, then the interview was conducted with a brother or a sister of the subject. In some cases, other family members were also consulted.

Each pedigree contains information on all of the first- and second-degree relatives and first cousins. Information was obtained regarding the vital status of these family members and all occurrences of esophageal cancer and other cancers. Current age, age at diagnosis of cancer, site of cancer (where applicable), age of death, clinical and pathological diagnosis of cancer were recorded for all first-degree relatives. The presence of parental consanguinity was recorded for cases and controls.

Most of the cases of esophageal cancer diagnosed in relatives were diagnosed by a local doctor using radiography (55%), or by endoscopy and pathology in an urban referral hospital (35%). A small number of affected relatives (10%) were considered to have died of esophageal cancer, because they suffered from dysphagia (swallowing difficulty) prior to death. The clinical symptoms of esophageal cancer are distinctive, and swallowing difficulty is the simplest symptom to use in the diagnosis of the disease. We could not obtain the pedigree for 13 cases and 20 controls, either because the address had been changed (26 subjects) or because they did not wish to participate (7 subjects), and these were excluded.

The study protocol was approved by ethics committee of Digestive Disease Research Center of Tehran University of Medical Sciences.

Statistical analysis

Based on the pedigree data, 2 cohorts were constructed, consisting of the 2,097 first-degree relatives of cases and the 2,783 first-degree relatives of controls. Each first-degree relative of the cases and controls was considered to be a study subject. Study subjects were followed until the occurrence of esophageal cancer, or death from another cause, or the date of the study interview. The exposed cohort was composed of the first-degree relatives of the cases, and the unexposed cohort was made up of the relatives of the controls. Cumulative hazard curves were constructed, which describe the cumulative incidence of being diagnosed with esophageal cancer over time. The occurrence of esophageal cancer among the relatives of cases and controls was compared for each familial relationship by using the Cox proportional hazards model.

Results

The characteristics of the cases and controls and their first-degree relatives are shown in Tables I and II, respectively. A total of 167 cases and their families were enrolled in this study. The mean age at diagnosis of cases was 64.7 years (range 31-90 years).

Sixty-nine patients were female (41.3%) and 98 patients were male (58.7%). At the date of interview, 97 patients had died (58.1%), on average 1.5 years after diagnosis, and 70 were alive (41.9%). The mean age of death was 66.2 years. Of the 200 controls, 107 were female (53.5%) and 93 were male (46.5%). Sixteen controls (8.0%) had died by the time of interview, and a relative (brother or sister) was interviewed. The causes of death in controls were accident, ischemic heart disease, cerebrovascular accident and infectious diseases. The mean age of death for controls was 67.4 years.

Table I. Comparison of Cases and Controls

Variables	Cases (*N* = 167)[1]	Controls (*N* = 200)[1]	*p*-value
Mean age of diagnosis[2]	63.6	-	-
Mean age if alive	64.1	60.4	0.03
Mean age at death	66.2	67.4	0.71
Gender			
Female	69 (41.3)	107 (53.5)	
Male	98 (58.7)	93 (46.5)	0.02
Ethnic subgroup			
Goglan	62 (37.1)	34 (17.0)	
Yamout	96 (57.5)	159 (79.5)	
Teke	6 (3.6)	3 (1.5)	
Atabay	3 (1.8)	4 (2.0)	<0.001
Vital Status			
Alive	70 (41.9)	184 (92.0)	
Dead	97 (58.1)	16 (8.0)	<0.001

[1] Values in parentheses are in percentages.

[2] Mean ages are in years.

Table II. Comparison of First-Degree Relatives of Cases and Controls

Variables	First-degree relatives of cases (*N* = 2,097)[1]	First-degree relatives of controls (*N* = 2,783)[1]	*p*-value
Mean age if alive[2]	36.4	37.3	0.13
Mean age at death	48.3	48.3	0.97
Gender			
Female	1,077 (51.4)	1,404 (50.6)	
Male	1,020 (48.6)	1,376 (49.4)	0.58
Ethnic subgroup			
Goglan	783 (37.3)	481 (17.3)	
Yamout	1,219 (58.1)	2,225 (80.0)	
Teke	66 (3.2)	28 (1.0)	
Atabay	29 (1.4)	49 (1.7)	<0.001
Vital status			

Alive	1,444 (69.0)	2,084 (75.0)	
Dead	650 (31.0)	693 (25.0)	<0.001
Missing	3	6	

[1] Values in parentheses are in percentages.

[2] Mean ages are in years.

Table III shows the numbers of cases and controls for whom at least 1 relative with esophageal cancer was reported. Esophageal cancer was significantly more common in the first-degree relatives of the cases than in those of the controls; 62.3% of the cases and 31.4% of the controls reported at least 1 first-degree relative with esophageal cancer (odds ratio = 3.6; $p = 2 \times 10^{-8}$). On average, the cases had 0.8 affected first-degree relatives, *versus* 0.4 of the controls ($p < 10^{-6}$). It is possible that the recollection of the number of affected relatives might differ depending on whether a cancer patient or a proxy respondent was interviewed. Sixty-five percent of the living cases reported 1 or more affected first- degree relatives, compared to 60% for proxy interviewers.

Table III. The Prevalence of Esophageal Cancer in One or More First-Degree Relatives of Cases and Controls

Relation	Proportion with one or more affected first-degree relatives		Odds ratio (95% CI)	*p*-value
	Cases (*N* = 167)[1]	Controls (*N* = 200)[1]		
All first-degree relatives	91 (62.3)	59 (31.4)	3.6 (2.3-5.7)	0.00000002
Parents	53 (39.3)	36 (19.4)	2.7 (1.6-4.4)	0.0001
Siblings	47 (29.2)	30 (15.5)	2.2 (1.3-3.8)	0.002
Children	3 (2.0)	1 (0.5)	3.7 (0.38-35.7)	0.33

Information on missing data was not included in the calculations of percentages.

[1] Values in parentheses are in percentages.

There were 2,097 first-degree relatives of the 167 cases and 2,783 first-degree relatives of the 200 controls (82 relatives were excluded because of missing data). Table IV shows the occurrence of esophageal cancer in these 2 groups. The cumulative risks of being affected by esophageal cancer at age of 75 for each cohort are shown in Table V, along with the corresponding hazard ratios. The cumulative risk of getting esophageal cancer in the first-degree relatives of the cases was 34% by the age of 75, compared to 14% for the relatives of controls (hazard ratio = 2.3; $p = 3 \times 10^{-8}$) (Fig. 1). The relatives of cases and controls were similar with respect to age and sex (Table II). However, there were significant differences in vital status and ethnic subgroups between the first-degree relatives of cases and controls. To adjust for possible confounding effects of these variables, the analysis was redone, adjusting for these in the Cox proportional hazards model. After adjustment, the hazard ratio was essentially unchanged (hazard ratio = 2.0; $p = 2 \times 10^{-6}$). Cases (9.6%) reported that their parents were related (most of them were first cousins), compared to 2.5% of the controls who reported this, most of whom were also first cousins (odds ratio = 4.1; $p = 0.006$).

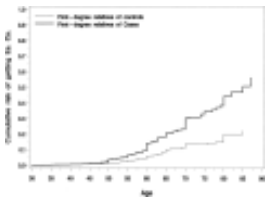

Figure 1. Comparison of cumulative risk of getting esophageal cancer in the first-degree relatives of cases and controls.
[Normal View 15K | Magnified View 36K]

Table IV. Occurrence of Esophageal Cancer in First-Degree Relatives of Cases and Controls

	Case relatives		Control relatives			
Relative	Affected	Total	Affected	Total	Odds ratio (95% CI)	*p*-value
Parents	65	282	39	379	2.6 (1.7-4.0)	0.00001
Mother	31	139	16	187	3.1 (1.6-5.9)	0.0007
Father	34	143	23	192	2.3 (1.3-4.1)	0.005
Siblings	63	646	42	1,076	2.7 (1.8-4.0)	0.000002
Sister	25	299	22	525	2.1 (1.2-3.8)	0.02
Brother	38	347	20	551	3.3 (1.9-5.7)	0.00002
Children	3	1,110	1	1,304	3.5 (0.37-24.0)	0.34

Table V. The Cumulative Risk of Esophageal Cancer by Age 75, and Associated Hazard Ratios for First-Degree Relatives

			Univariate		Multivariate*	
Relation	Risk to age 75 for case relatives (%)	Risk to age 75 for control relatives (%)	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
All first degree relatives	34	14	2.3 (1.7-3.1)	3×10^{-8}	2.0 (1.5-2.7)	2×10^{-6}
Parents	45	14	2.9 (1.9-4.4)	1×10^{-6}	2.4 (1.5-3.8)	1×10^{-4}
Siblings	28	15	2.0 (1.3-3.0)	0.001	1.7 (1.1-2.6)	0.01
Male relatives	34	13	2.3 (1.5-3.5)	6×10^{-5}	2.1 (1.4-3.1)	8×10^{-4}
Female relatives	34	14	2.3 (1.5-3.5)	0.0001	2.0 (1.3-3.1)	0.002

* **Adjusted for ethnicity and vital status.**

The risk of esophageal cancer in the siblings of the cases to age 75 was then estimated, stratifying by the number of affected parents. For patients with none or 1 affected parent, the sibling cumulative risk was 19%, and for patients with 2 affected parents, the risk was 46% ($p = 0.004$) (Fig. 2).

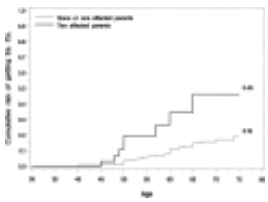

Figure 2. Comparison of cumulative risk of getting esophageal cancer in the siblings of cases with none or one and two affected parents.
[Normal View 14K | Magnified View 34K]

Discussion

The large variation in the incidence of esophageal cancer in different geographic regions has often been thought to be due to

variation in exposure to environmental factors; however, our results suggest that hereditary factors may also contribute to the variation in rates. In particular, genetic factors appear to be important in the high incidence area of northeastern Iran.

In some families, esophageal cancer appears as a hereditary trait. For example, in one family, there were 17 patients reported to have esophageal cancer (Fig. 3). Overall, we identified 39 families (22 cases, 17 controls) with 4 or more patients with esophageal cancer. Families of this type are likely to segregate a high penetrance cancer susceptibility allele, and should be suitable for linkage analysis. However, because of the high case-fatality of the disease, few living, affected relatives are available for study. Furthermore, 58% of our probands had died, on average 18 months following diagnosis.

Figure 3. A Turkmen family with aggregation of esophageal cancer (individuals in black color represent patients with esophageal cancer and the number below it is the age of diagnosis).
[Normal View 9K | Magnified View 20K]

Although it was not possible to determine the pathologic type of the esophageal cancer in the relatives, based on previous reports, more than 90% of these esophageal cancers should be of the squamous cell type.[10]

Esophageal cancer was more common in both the parents and siblings of the patients with the disease (there were too few affected children to study this category separately), and the hazard rates were similar. These observations suggest a dominant pattern of transmission with incomplete penetrance. However, parental consanguinity was much more common in cases than in controls - consistent with an autosomal recessive mode of inheritance. It is also necessary to consider more complex patterns of inheritance, such as a multiple gene model or a pseudo-dominant condition (the latter would arise if the trait were recessive but were due to a very common allele in the population).

The risk to age 75 of esophageal cancer in the control relatives was 14%. This is essentially an estimate of the risk of esophageal cancer in unselected Turkmen from the region, and attests to the very high incidence rate of the disease and the potential role of environmental exposures. The risk was similar for male (13%) and female (14%) first-degree relatives. In contrast, in North America, the risk of esophageal cancer to age 75 is reported to be only 0.3%, or about 50 times less. In North America, esophageal cancer is much more common in men than in women, and rates are higher in African-Americans than in whites. In our study, the highest rate was observed for individuals with a sibling and both parents affected; under this scenario, the risk to age 75 approached 50%. We observed similar risks among the first-degree relatives of patients belonging to the different ethnic subgroups (data not shown).

Our results are similar to those which were reported from a high incidence area in China.[20][21][22][23][24][25][26] Two case-control studies were conducted in high-incidence area in China. One of them found that the risk of esophageal cancer was increased to 70%, if there was a history of esophageal cancer or stomach cancer in a parent.[20] Another study reported that the relative risk was 2.0, when any relative was affected.[21]

A population-based case-control study (167 cases, 820 controls), which was conducted in low-risk area in Sweden, reported no significant association between a family history of esophageal cancer and the risk of cancer of any histological type.[27] However, a more recent nation-wide Swedish study based on a family-cancer database containing 10.1 million individuals and nearly 6,000 esophageal cancer patients reported a standardized incidence ratio of 3.9 when a parent was diagnosed with esophageal cancer, and 12.6 when a sibling was affected.[28] This attests to the necessity of having a large sample to study, because of the rarity of the condition in the west. Studies from other low-risk areas, such as the United States, have not identified family history to be a risk factor. A case-control study of esophageal cancer (all histological types) from North Carolina did not identify any familial link.[29] In a second study from New York, none of 139 male patients with esophageal squamous cell carcinoma had a positive family history of esophageal cancer.[30]

This contrast between the high- and low-risk countries may be due to variation in the frequency of esophageal susceptibility alleles, or due to variation in environmental risk factors, or due to a combination of the two. In the west, risk factors include male sex, smoking, and alcohol use[3] and these are not risk factors in Iran. Future studies will provide information about the relative contribution of genetic and environmental factors in the development of esophageal cancer in Iran.

There are several strengths to this study. It has been known since the 1970s that this geographic region has a high incidence of esophageal cancer. The Turkmen population is stable and genetically homogenous. All of the cases with esophageal squamous cell carcinoma were diagnosed by endoscopic and pathologic evaluation. Detailed family histories were obtained by going to the house of proband and interviewing several family members. Unfortunately, it was not possible to obtain pathological confirmation of the diagnoses of esophageal cancer in the relatives, and some diagnoses may have been missed. Also, in many cases, the proband had died and it was necessary to interview a close relative. However, this did not seem to result in a recall bias, because the average number of affected relatives reported was similar for cases and for proxy respondents. Futhermore, adjustment for

vital status of the case did not materially affect the odds ratio.

In summary, this study confirms that there is a strong familial component to esophageal cancer etiology among the Turkmen population of Northern Iran. Future studies are planned with the hope of identifying the susceptibility alleles responsible for this association.

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