Original Article

Family History as a Risk for Upper Gastrointestinal Tract Cancer: A Case Control Study

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Abstract

Background: Although, family history of cancer is an important risk factor for upper gastrointestinal cancers development, but limited information is available on the upper gastrointestinal cancers associated with family history in Iran. The purpose of this study was to define upper gastrointestinal cancers risk associated with family history of cancer.

Methods: This study was conducted as a case control study. A total number of 1,010 cases of upper gastrointestinal cancer and 1,010 healthy controls were recruited. For family history of cancer, questions were asked about any malignant tumor in first and second degree relatives. Adjusted odds ratio estimates for the association family history and upper gastrointestinal cancers risk and corresponding 95% confidence intervals were obtained.

Results: A family history of any malignant tumor in relatives was associated with 1.3 fold increased risks of upper gastrointestinal cancers. A first-degree family history of esophageal and gastric cancer was significantly associated with upper gastrointestinal cancers development, with an adjusted OR of 4.7(CI 95%: 2.6-8.4).

Conclusion: Our findings suggested that risk for upper gastrointestinal cancers increases among individuals with family history of cancer. Therefore, appropriate screening strategies especially in relatives of patients should be considered to prevent and control of disease.

Key Words: Upper gastrointestinal tract; Gastrointestinal neoplasm; Esophageal neoplasm, Case-Control Study

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Introduction

Malignancies of the upper gastrointestinal (UGI) tract form a heterogeneous group of cancers characterized by unique epidemiology and biology[1]. They are much more common in Asia than in western countries.[2-4]. Upper gastrointestinal cancers cause 55% of all cancer-related deaths in Iran, with gastric cancer being the most common[5]. Although the incidence of gastric cancer (GC) has declined in the past several decades, it remains the second most common cause of cancer-related deaths in the world[6, 7]. Gastric cancer is an important cause of mortality due to cancer and is predict to be the eighth leading cause of all death worldwide in the year 2010[8]. GC is the most common malignancy in Iran[9-11]. In recent years, cancer morbidity and mortality increased in Iran, and GC is ordered second among all cancers in this country[12-14].

Also, esophageal cancer (EC) is among the 10 most common tumors and is the 6th leading cause of malignancy deaths worldwide[2, 15]. The incidence rate appears to have decreased during the last 3 decades but is still 6th common cancer in Iran.

A number of environmental factors are now known to be related to the development of the GC[16].Smoking, alcohol consumption, Helicobacter pylori infection, dietary habits and obesity may be risk factors of gastric cancer[6]. However, neither the relative risks associated with these factors nor their prevalence in the Iranian population is of appropriate magnitude to justify the extremely high incidence. It is therefore important that familial factors also be considered as possible risk factors contributing to the development of GC[17]. Most

epidemiologic studies reported a risk of gastric cancer between 1.5 and 3.5 for subjects with relatives with gastric cancer[17].

The principle risk factors for esophageal cancer are thought to be environmental. Smoking, alcohol consumption, a dietary deficiency of fruits and vegetables, the consumption of very hot beverages and exposure to carcinogens due to opium consumption as have been stressed important risk factors, but recently the genetic nature of esophageal cancer has received much attention[4]. One study from Iran showed that subjects with one or more first degree relatives with esophageal cancer have a odds ratio of developing esophageal cancer about 3.5[4].

It has been suggested that familial esophageal cancer may develop earlier and have a poorer prognosis than sporadic esophageal cancer. Therefore, it is reasonable to hypothesize that FH of cancer might also predict survival of upper gastrointestinal cancer[18].

Family history (FH) by different relative types and risk of UGI cancers has been only rarely reported in Iran[4, 19]. Therefore, this study was under taken to confirm the impact of familial susceptibility on UGI cancer development.

Materials and Methods

This research was conducted in Research Institute for Gastroenterology and Liver Disease (RIGLD), Shahid Beheshti University of Medical Science, Tehran capital of Iran, as a case control study. A total number of 1,010 cases of UGI cancer and 1,010 healthy controls were recruited. We included cases in this study who: had their diagnosis histologically confirmed without previous history of cancer. Controls were randomly selected among the healthy participants in a health survey conducted by the Department of Health System Research of RIGLD in that a total of 5,500 subjects aged≥15 years were invited to participate in an interview about the occurrence of cancer in their first- or second-degree relatives[20, 21].

After obtaining informed consent, both cases and controls were interviewed to obtain information on demographic characteristics, and FH. For FH of cancer, questions were asked about any malignant tumor in first degree relatives, including father, mother, siblings, and offspring. In addition, information on cancer history was also collected on second degree relatives as the cases and controls (i.e., grand father or mother, aunt and uncle).

The FH was extracted from a standard history form completed by the patient or from the record created by a health care provider. The ethical committee at Shahid Beheshti University of Medical Sciences approved the study.

Adjusted odd ratio(OR) estimates for the association FH and UGI cancers risk and corresponding 95% confidence intervals were obtained. To account for potential confounders, multivariate logistic regression analyses were conducted. All the regression models included terms for age and sex. Statistical analysis was performed with SPSS (version 13.0). All analyses were two-sided, and statistical significance was defined as a P-value less than 0.05.

Results

A total of 2,020 cases and controls were enrolled in this study. The mean (± SD) age of cases was 53.8±18.6 years. 68.1% of patients were male. Of the 1,010 controls, 529 (52.4%) were female and 481(47.6%) were male. By design, the proportion of men was higher in cases than in controls, and the age distribution was higher in cases (P-value is $P<0.0001$).

Two hundred twenty two (22%) of cases and 237 (23.5%) of controls reported the occurrence different types of malignant tumors in their family members ($P>0.05$). A FH of any malignant tumor in relatives was associated with 1.3 fold increased risks of UGI cancers (Table 1).

Table 2 presents the distribution of UGI cancers in the first-degree relatives of cases and controls. A first-degree family history of esophageal and gastric cancer was significantly associated with UGI cancers development, with an adjusted OR of 4.7 (CI 95%: 2.6-8.4). Overall, 3.5% of cases versus 2.5% of controls reported a family history of UGI cancer in second degree relatives. Results indicating that having a positive family history of UGI cancer in second degree relatives increase one's risk of UGI cancer about 3 fold.

None of the other cancer sites in relatives showed a significant association with risk of UGI cancers (Table 3).

Discussion

In present case-control study focusing on FH of cancer and risk of UGI cancers, we observed increased risk for UGI cancers among individuals with FH of any malignant tumor and UGI cancers. The excess risk was most apparent for first degree relatives compared to second degree relatives. This result is in agreement with another studies[4, 18].

Some studies suggest that FH increases the risk of cancer at many sites and is not site-specific [22]. The

Table1. Associations between family history of any malignant tumor and risk of UGI cancers

	Cases	Controls	Crude OR	Adjusted OR+
	n (%)	n (%)	(CI: 95%)	(CI: 95%)
Family history of Cancer				
FDR*/SDR**				
No	788(78.0)	773(76.5)	0.94(0.78-1.12)	1.3(1.01-1.66)
Yes	222(22.0)	237(23.5)		
FDR				
No	864(85.5)	896(88.7)	1.28(1.01-1.64)	1.24(0.92-1.68)
Yes	146(14.5)	114(11.3)		
SDR				
No	918(90.9)	872(86.3)	0.63(0.48-0.84)	1.27(0.90-1.78)
Yes	92(9.1)	138(13.7)		

* Family history of cancer in First Degree Relatives
** Family history of cancer in Second Degree Relatives
+ Adjusted according to age and sex

Table2. Associations between family history of UGI malignant tumor and risk of UGI cancers

	Cases	Controls	Crude OR	Adjusted OR+
	n (%)	n (%)	(CI: 95%)	(CI: 95%)
Family history of UGI malignancy				
FDR/SDR				
No	910(90.1)	970(96.0)	2.5(1.73-3.61)	3.67(2.34-5.76)
Yes	100(9.9)	40(4.0)		
FDR*				
No	935(92.6)	993(98.3)	4.68(2.75-7.99)	4.67(2.60-8.41)
Yes	75(7.4)	17(1.7)		
SDR**				
No	974(96.4)	985(97.5)	1.44(0.86-2.39)	2.81(1.49-5.32)
Yes	36(3.6)	25(2.5)		

* Family history of cancer in First Degree Relatives
** Family history of cancer in Second Degree Relatives
+ Adjusted according to age and sex

Table3. Associations between family history of any malignant tumor except esophageal and gastric cancer and risk of UGI cancers

	Cases	Controls	Crude OR	Adjusted OR+
	n (%)	n (%)	(CI: 95%)	(CI: 95%)
Family history of other Cancer				
FDR/SDR				
No	880(87.1)	801(79.3)	0.62(0.50-0.77)	0.80(0.61-1.06)
Yes	130(12.9)	209(20.7)		
FDR*				
No	928(91.9)	912(90.3)	0.84(0.62-1.12)	0.74(0.53-1.66)
Yes	82(8.1)	98(9.7)		
SDR**				
No	947(93.8)	889(88.0)	0.52(0.38-0.71)	1.03(0.70-1.51)
Yes	63(6.2)	121(12.0)		

* Family history of cancer in First Degree Relatives
** Family history of cancer in Second Degree Relatives
+ Adjusted according to age and sex

association between FH and UGI cancer risk in present survey strengthened as FH became more specific: OR=1.3 for FH of any cancer, OR=3.67 for FH of UGI cancer. Our estimated OR is higher than one Chinese study[18]. Differences from previous reports could be due to variation in the prevalence of UGI cancers in the study populations. In contrast, no association was observed between FH of non-UGI cancer and risk of UGI cancer. This suggests that the shared susceptibility is UGI specific, and FH of non-

UGI cancer is not important for UGI cancer risk prediction[17, 18].

A number of previous studies reported increased risk of gastric cancer among individuals with a positive family history of cancer [17, 23]. Only a few studies have been examined the risk of gastric cancer by anatomic sub sites (cardia and non-cardia)[24] . FH of gastric cancer was associated with increased risk of non-cardia cancer only, and FH of any cancer was associated with increased risk of cardia cancer only[24]. Ying Gao et al. [18] found that FH of gastric cardia cancer was associated with increased risk for both gastric cardia and gastric non-cardia adenocarcinoma, but no association was observed between FH of gastric non-cardia cancer and risk of either gastric non-cardia adenocarcinoma or gastric cardia adenocarcinoma.

It is suggest that younger age at onset is often related with genetic role in disease. Wen et al.[25] With a case-control study showed that, FH correlated with early age of onset for esophageal cancer. Garavello et al. [16,26] found also that younger individuals with a FH of cancer have higher risks for development of cancer. In this study we don't have access to the age of onset of disease.

Although, inherited susceptibility is a very important risk factor in UGI cancers , but co-occurrence of UGI cancers among family members does not necessarily reflect shared genetic susceptibility; it could also be due to shared environmental exposures[17, 18, 27]. Therefore, studying different types of relatives (blood and non-blood relatives sharing household) might provide information to help differentiate genetic and environmental components in esophageal and gastric pathogenesis. While several studies have reported that environmental factors like may play a more important role than genetic factors in UGI development[4] some studies haven't found a strong correlation between FH of UGI and environmental factors, such as lifestyles[28]. This contrast may be due to variation in the frequency of esophageal and gastric susceptibility alleles, or due to variation in environmental risk factors, or due to a combination of the two[1, 4]. In the west countries, risk factors include male sex, smoking, and alcohol use, and these are not risk factors in Iran. Further studies will provide information about the relative contribution of genetic and environmental factors in the development of UGI cancers in Iran.

Limitations of this study are: potential recall bias due to the nature of the case-control study design. Information on family history was self-reported, and it is possible that cases of GC and EC may tend to recall a FH of UGI cancer or other cancers more accurately than controls. Aggregation of cancer among non-blood relatives in the same household, like wives and husbands, supports environmental compared to genetic factors in cancer etiology. But we don't access to information about non-blood relatives and also about number of first and second degree relatives affected. Also, unfortunately, it was not possible to obtain pathological confirmation of the diagnosis of cancer in the relatives, and some diagnosis may have been missed. Another limitation of this study is potential misclassification bias. Different diagnostic criteria and classification methods may have led to incorrect designation of tumor location and histology for a proportion of patient. So the interpretation and generalization results of this study should be done with caution.

A strong point of this study is the large and representative sample. Another strong point of the study is that we conducted multivariate analyses, which allowed us to control the effects of confounder factors in analysis.

Conclusion

Our findings suggested that risk for UGI cancers increases among individuals with family history of cancer. Future studies will provide information about the relative contribution of genetic and environmental factors in the development of upper gastrointestinal cancers in Iran. We support the establishment of a national program to investigate potential risk factors for UGI cancers by tumor site and possible gene-environment interactions in patients from different racial groups. Such analysis may help us to better understand the epidemiology of UGI cancers and provide a basic foundation for developing prevention strategies among individuals at high risk.

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Conflicts of Interest

None to declare.

Authors' Contribution

AS conceived and designed this study and interpreted the results and drafted the manuscript. BMD designed and carried out the analyses. SRF

revised the manuscript. FGH and EM contributed to data gathering and data entering to the software. MRZ supervised the project. All authors read and improved the final manuscript.

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