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Original Article

Risk of Gastric Cancer is Highly Dependent on Type of First-Degree Family Member Affected by Cancer: Lessons from a High-Risk Population in Iran

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Abstract

Background: Family history of gastric cancer (GC) in first-degree relatives may increase the risk of GC. This study aimed to assess how family history of GC in first-degree relatives really affects the risk of GC in an extremely high-risk population.

Methods: A large population-based case-control study was carried out on 1222 incident GC cases and 1235 controls in Ardabil Province-a high-risk area in North-West Iran-to assess the associations of GC family history in first-degree relatives with the risk of GC (2003-2017).

Results: GC family history did not significantly associate with the risk of GC overall (OR_{adj}=1.09, 95% CI: 0.80–1.47, *P*=0.589). It found no significant association of GC family history in a parent, and in a father, mother, and sister separately, with the risk of GC. However, GC risk was significantly associated with a history of GC in a sibling (OR_{adj}=1.61, 95% CI: 1.11–2.35, *P*=0.013), especially brother (OR_{adj}=2.24, 95% CI: 1.41–3.64, *P*=0.0008). The risk was greatly increased in subjects with two or more affected brothers (OR_{adj} =5.56, 95% CI: 2.33–14.20, *P*=0.0002).

Conclusion: We did not find a familial tendency to cardia GC and non-cardia GC as well as histopathologic features. Determining the type of first-degree relationships with GC may, therefore, be more important than assessing family history alone for predicting the risk of GC in this high-risk area.

Keywords: Gastric cancer; High-risk area; Family history; First-degree relatives; First-degree relatives

Introduction

Gastric cancer (GC) is the fifth most popular type of cancer (6.8%) in the world and the third leading cause of cancer deaths (8.8%) (1). With respect to global estimates in 2012, there were

952,000 patients with GC. Two-thirds of the patients were men and one-third were women, corresponding to the GC ASRs of 17.4/100,000 and 7.5/100,000, respectively (2). There are two GC subtypes, cardia gastric adenocarcinoma and non-cardia gastric adenocarcinoma (3). Gastric adenocarcinoma is classified into two major histologic subtypes; intestinal and diffuse adenocarcinoma (Lauren's classification) (4). Four molecular subtypes of GC have been recently determined, which comprise Epstein–Barr virus (EBV), microsatellite instability (MSI), gnomically stable (GS), and chromosomal instability (CIN) (5). CIN subtype, mostly occurring in the esophagogastric junction/cardia, is associated with intestinal-type histology (6).

GC is caused by the complex interaction of *Helicobacter pylori* infection, genetic and epigenetic abnormalities, and environmental conditions (7-9). About half of the world's population are infected with *H. pylori*; however, a low number of the infected individuals develop non-cardia GC (NCGC), indicating that host genetic elements have a significant role in gastric carcinogenesis (7). Family history is the most common risk factor for GC; however, the molecular origin for familial aggregation is not clear. Nevertheless, 10% of GC cases are related to the hereditary cancer category, instead, only 1%-3% of gastric carcinomas is developed due to an inherited GC predisposition syndrome. Patients with GC show a 2- to 3-fold greater rate of family history, indicating that GC family history is an independent risk factor (10). Although GC rates vary across the world, family history as a GC risk factor is very common. Hence, the specification of high-risk individuals is significant for the prevention and surveillance of GC.

Ardabil Province is a mountainous and volcanic region in the Northwest of Iran, West Asia. It is composed of a homogeneous Azeri ethnic group (98%) with the highest *H. pylori* infection rate (89%). Ardabil has the highest GC rate in Iran (ASRs, 51.8/100,000 and 24.9/100,000 for males and females, respectively) and one of the highest cardia GC (CGC) rates worldwide. The cardia subsite incidence was, 26.4 and 8.6 for men and women, respectively (11, 12). The higher number of GC incidence in Ardabil results from the higher CGC rate compared to the rate of NCGC. The large proportion of CGC in Ardabil is reported on the right side rather than the left side (or greater curvature) (13). There is little information about how family history really affects the risk of GC worldwide, especially in a high-risk large population. We, therefore, used the most recent data from Ardabil to test whether GC family history in first-degree relatives correlates with a risk of GC or not. We also performed additional analyses considering the type and number of first-degree relatives as well as site-specific subtypes and GC histology.

Materials and Methods

Study population

A large population-based case-control study was performed on 1222 adult GC patients randomly selected at the start of study from data available (2003-2017) in the Cancer Registry Center in Ardabil Province, Iran. We used Random Number Generator to select cases. There was a complete information about cases in the cancer registry and Aras's clinic, which is a clinic of Digestive Disease Research Center in the University.

The general inclusion criteria for cases were as follows: I) Ardabil residents for at least 10 years before diagnosis, II) aged more than 18 yr, III) without previous history of gastric surgery, and IV) a positive histopathologic report. We diagnosed gastroduodenal disease according to endoscopic and histopathologic results. GC diagnoses were categorized by anatomic subsites based on the International Classification of Diseases (Ninth Revision (ICD-9)), as cardia (ICD-9 code 151.0) and non-cardia (ICD-9 codes 151.1–151.9, involving unspecified and overlapping subsites). The tumors originated from above the *Z*-line were considered as esophageal adenocarcinoma, but not CGA, and excluded from the analysis. Histologic subtypes were examined as intestinal-type, diffuse-type, and other/unspecified histologies, based on the classification of Lauren. Partic-

ipants with the pathologic diagnosis of MALToma or no-tumors were excluded from the analyses. Control subjects (n=1235) were from the cohort on the effect of low-dose aspirin on the incidence and mortality of GC in the Northwest of Iran. They were randomly selected at the start of study from community within age and sex strata according to their records at the health center and assumed to be cancer-free. As the 96% of Ardabil residents have been recorded in a database, the selected people could be the representative of the whole society. It was 5-year age group. Therefore, we used age frequency matching. Controls also had to be a resident of Ardabil province for at least 10 yr and had the same criteria as cases except for being a GC patient.

Data collection

Subjects were invited to the research center and in the case of their acceptance; they were included in the study. We applied a structured questionnaire during the in-person interviews for data collection considering the following variables; age at diagnosis, gender, histopathologic types, tumor location, and first-degree family cancer history. Subjects were asked to report if their parents, siblings or children had been suffered from GC. Information on the number of full-brothers, full-sisters, and non-adopted children living or deceased were also recorded.

Statistical analysis

Unconditional logistic regression models used adjusted odds ratios (OR) for age and sex (95% confidence intervals (CIs)) to assess the associations between GC family history in first-degree relatives and the risk of GC. We assessed the risk associated with GC family history for the type of first-degree relationship (i.e., parent, father, mother, sibling, brother, and sister), and for each anatomic subsite (cardia and non-cardia) and histologic feature (intestinal- and diffuse-type) of cancer. We tested whether cases and controls differed with respect to the number of first-degree relatives with GC overall, and the number of affected siblings and affected brothers and sisters separately (0, 1, or =>2). In multiple comparisons, we have an increased probability of false positives. We, therefore, estimated the false discovery rate (FDR) (14) among the associations tested. It determines adjusted P-values for each test and controls the number of false discoveries among the set of significant results. All models had terms for age (in year) and gender. The p-values were assumed significant at P<0.05. Software R 3.5.2 was applied for all statistical analyses.

Ethical approval

The study was approved by the ethics committees of the National Institute for Medical Research Development/IR.NIMAD.REC.1396.097, Tehran, Iran, and the Ardabil University of Medical Sciences/IR.ARUMS.REC.1396.160, Ardabil, Iran, based on the ethical principles of human research and experimentation expressed in the 1964 Declaration of Helsinki and its later amendments. Informed consent for participation in the study was given by each subject in writing. All the authors have read and approved the final manuscript.

Results

The GC group included 1222 patients; average age was 64.03 (males 63.72; females 64.67). Overall, 7.86% had a positive GC family history in their first-degree relatives; average age was 65.79. The control group included 1235 individuals; average age was 62.75 (males 62.51; females 63.22). 7.21% had a positive GC family history; average age was 64.36. Age-distribution of the population was summarized in Table 1.

The GC patients' prevalence based on the anatomic site of the tumor origin was 41.32% (505/1222) with CGC, 48.93% (598/1222) with NCGC, and 9.73% (119/1222) with both the CGC and the NCGC. According to histopathologic features, the prevalence of the intestinal-, the diffuse-, and the indeterminate-types was 65.71% (803/1222), 30.93% (378/1222), and 3.35% (41/1222), respectively. In patients with a family history of GC in first-degree relatives, the

prevalence of CGC, NCGA, and both the CGC and the NCGC, was 36.45% (35/96), 51.04% (49/96), and 12.5% (12/96), respectively. Prevalence of the intestinal-, the diffuse-, and the indeterminate-types was 69.79% (67/96), 27.08% (26/96), and 3.12% (3/96), respectively.

Table 1: Age-distribution (year) of the study population

Variable	*Case (%)*	*Control (%)*	*Total*
<=35	12 (37.5)	20 (62.5)	32
36 - 40	23 (42.6)	31 (57.4)	54
41 - 45	35 (43.8)	45 (56.3)	80
46 - 50	61 (46.4)	67 (53.6)	128
51 - 55	112 (49.3)	115 (50.7)	227
56 - 60	171 (49.0)	178 (51.0)	349
61 - 65	238 (48.7)	251 (51.3)	489
66 - 70	264 (50.9)	255 (49.1)	519
71 - 75	151 (52.6)	136 (47.4)	287
76 - 80	84 (48.8)	88 (51.2)	172
81 - 85	41 (54.7)	34 (45.3)	75
86 - 90	21 (61.8)	13 (38.2)	34
> 90	4 (44.4)	5 (55.6)	9
NR*	7 (100.0)	0 (0.0)	7
Total	1222 (49.74)	1235 (50.26)	2457
*not reported			

Overall, GC family history did not significantly associate with the risk of GC (OR_{adj} = 1.09, 95% CI: 0.80 – 1.47, *P*=0.589), whether in males or females. It found no significant association between GC family history in a parent (father or mother), and in a father, mother, and sister separately, and GC risk (*P*>0.05). GC risk also was not significantly associated with increasing the number of affected first-degree relatives overall (*P*>0.05). However, GC risk was significantly associated with a history of GC in a sibling (OR_{adj} =1.61, 95% CI: 1.11–2.35, *P*=0.013), especially brother (OR_{adj}=2.24, 95% CI: 1.41–3.64, *P*=0.0008; Table 2).

The risk was further increased when two or more siblings suffered from the disease (OR_{adj}=2.97, 95% CI: 1.52–5.99, *P*=0.0017). The risk also increased with one affected brother but increased more when two or more brothers were affected (OR_{adj}=5.56, 95% CI: 2.33–14.20, *P*=0.0002; Table 3).

We did not find such a pattern for two or more affected sisters (*P*>0.05; Table 3). Moreover, first-degree family history of GC did not associate with the risk of cardia and non-cardia GC and their histologic subtypes (intestinal and diffuse) (Table 4).

Table 2: Association between GC family history and risk of gastric cancer

GC family history		*No. of Cases (%)*	*No. of Controls (%)*	*Adjusted OR[b] (CI[c])*	*P-value*	*FDR-adjusted P-value*
Overall FH[a]						
	Negative	1126	1146	1 (ref)		
	Positive	96 (7.86)	89 (7.21)	1.09 (0.80 – 1.47)	0.5895	0.7859
Males						
	Negative	755	770	1 (ref)		
	Positive	60 (4.91)	50 (4.05)	1.23 (0.83 – 1.82)	0.2969	0.2969
Females						
	Negative	371	376	1 (ref)		
	Positive	36 (2.95)	39 (3.16)	0.90 (0.56 – 1.45)	0.6694	0.6694
Parental history						
	Negative	1195	1190	1 (ref)		
	Positive	27 (2.21)	45 (3.48)	0.63 (0.39 – 1.03)	0.0673	0.0897
Father history						
	Negative	1203	1204	1 (ref)		
	Positive	19 (1.55)	31 (2.51)	0.66 (0.36 – 1.16)	0.1581	0.2108
Mother history						
	Negative	1214	1220	1 (ref)		
	Positive	8 (0.65)	15 (1.21)	0.55 (0.22 – 1.28)	0.1805	0.4633
Sibling history						
	Negative	1146	1188	1 (ref)		
	Positive	76 (6.22)	47 (3.80)	1.61 (1.11 – 2.35)	0.0132	0.0176
Brother history						
	Negative	1164	1209	1 (ref)		
	Positive	58 (4.75)	26 (2.11)	2.24 (1.41 – 3.64)	0.0008	0.0032
Sister History						
	Negative	1199	1213	1 (ref)		
	Positive	23 (1.88)	22 (1.78)	0.99 (0.55 – 1.82)	0.9886	0.9886
No. of first-degree relatives						
	None	1126	1146	1 (ref)		
	1	85 (6.96)	84 (6.80)	1.13 (0.87 – 1.48)	0.3641	0.4855
	2+	11 (0.90)	5 (0.40)	1.28 (0.75 – 2.20)		
Total		1222	1235			

[a]FH, any first-degree relative; [b]OR, adjusted for both age and gender; [c]CI, confidence interval.

Table 3: The risk associated with GC family history for the number of affected siblings and affected brothers and sisters separately

Variable		*No. (%)*			
No. of siblings with GC (%)					
Cases					
	Males	769 (94.36)	42 (5.15)	4 (0.49)	815 (100)
	Females	377 (92.63)	23 (5.65)	7 (1.72)	407 (100)
	Total	1146 (93.78)	65 (5.32)	11 (0.90)	1222 (100)
Controls					
	Males	797 (97.20)	23 (2.80)	0 (0.00)	820 (100)
	Females	391 (94.22)	23 (5.54)	1 (0.24)	415 (100)
	Total	1188 (96.19)	46 (3.73)	1 (0.08)	1235 (100)
Adjusted OR[a]		1.00	1.72 (1.23 – 2.45)	2.97 (1.52 – 5.99)	*P* = 0.0017 *FDR-adjusted P-value=0.0087*
No. of brothers with GC (%)					
Cases					
	Males	777 (95.34)	36 (4.42)	2 (0.24)	815 (100)
	Females	387 (95.09)	16 (3.93)	4 (0.98)	407 (100)
	Total	1164 (95.25)	52 (4.26)	6 (0.49)	1222 (100)
Controls					
	Males	805 (98.17)	15 (1.83)	0 (0.00)	820 (100)
	Females	404 (97.35)	11 (2.65)	0 (0.00)	415 (100)
	Total	1209 (97.89)	26 (2.11)	0 (0.00)	1235 (100)
Adjusted OR		1.00	2.36 (1.53 – 3.77)	5.56 (2.33 – 14.20)	*P* = 0.0002 *FDR-adjusted P-value=0.0009*
No. of sisters with GC (%)					
Cases					
	Males	805 (98.77)	10 (1.23)	0 (0.00)	815 (100)
	Females	394 (96.81)	12 (2.95)	1 (0.24)	407 (100)
	Total	1199 (98.12)	22 (1.80)	1 (0.08)	1222 (100)
Controls					
	Males	812 (99.02)	8 (0.98)	0 (0.00)	820 (100)
	Females	401 (96.63)	14 (3.37)	0 (0.00)	415 (100)
	Total	1213 (98.22)	22 (1.78)	0 (0.00)	1235 (100)
Adjusted OR		1.00	1.06 (0.59 – 1.91)	1.13 (0.35 – 3.63)	*P*-value = 0.8391 *FDR-adjusted P-value=0.8611*

[a]OR, adjusted for both age and gender

Table 4: Association between GC family history and the risk of cardia and non-cardia GC and their histologic subtypes (intestinal and diffuse)

GC family history		*No. of Cases (%)*	*Adjusted OR[a] (CI)*	*P-value*	*FDR-adjusted P-value*
Cardia gastric cancer					
	Negative	470	1 (ref)		
	Positive	35 (6.93)	0.94 (0.62 – 1.40)	0.777	0.777
Non-cardia gastric cancer					
	Negative	549	1 (ref)		
	Positive	49 (8.19)	1.15 (0.80 – 1.66)	0.440	0.440
Intestinal-type GC					
	Negative	736	1 (ref)		
	Positive	67 (8.34)	1.13 (0.81 – 1.58)	0.456	0.608
Diffuse-type GC					
	Negative	352	1 (ref)		
	Positive	26 (6.88)	0.97 (0.60 – 1.50)	0.883	0.978
Total		1222			

Missing observations were removed. [a]OR, adjusted for both age and gender

Discussion

In the present study, GC family history did not significantly associate with the risk of GC overall (OR_{adj}, 1.09). It found no significant association of GC family history in a parent, and in a father, mother, and sister separately, with the risk of GC. However, GC risk was significantly associated with a history of GC in a sibling (OR_{adj}, 1.61), especially brother (OR_{adj}, 2.24). The risk was greatly increased in subjects with two or more affected brothers (OR_{adj}, 5.56).

Although most GC cases are sporadic, nearly 10% show familial aggregation (15). Family history of GC is a critical GC risk factor. Hereditary diffuse gastric cancer **(**HDGC) is the most common familial GC (16). Hereditary cancers are merely related to less than 3% of GC cases (17). Similarly**,** the present study showed that 7.86% of GC patients had a positive family history of GC. In males, although OR was estimated to be 1.23, the difference was not significant. In addition, the risk of GC was not significantly associated with increasing the number of affected first-degree relatives overall. In this regard, familial risks were higher in low-risk regions compared to high-risk regions, suggesting that genetic factors are possibly more prevalent in low CC risk populations (10). Therefore, both environmental and genetic factors may affect gastric carcinogenesis and contribute to the familial tendency.

In the current study, we did not find significant associations of GC family history in a parent, and in a father, mother, and sister separately, with the risk of GC, which is in inconsistent with previous studies (10, 18-21). Moreover, we found no significant relationship between GC family history in a sister and the risk of GC, even when two or more affected sisters were analyzed (OR, 1.04). Possessing two or more first-degree relatives with GC significantly associated with a higher risk of GC development compared to having only one first-degree relative (OR, 5.5 vs. OR, 1.7) (10). GC risk was significantly associated with an affected sibling (OR, 1.61), especially brother (OR, 2.24). We found a further increase in subjects having two or more affected siblings (OR, 2.78), especially brothers (OR, 5.47). Having a sibling (HR, 2.05) or a father (HR, 1.67) with GC increases the GC risk significantly (21). A study on an Italian population found that a sibling GC history is highly associated with increased GC susceptibility compared to a GC history in a parent (OR, 2.6 vs. OR, 1.7). The adjusted risk of GC was more in individuals with an affected mother compared to those with an affected father (OR,

2.3 and 1.3, respectively) (10), which is not in line with most previous studies (18-20).

Our study showed that GC family history in first-degree relatives did not associate with the risk of cardia and non-cardia GC or intestinal- and diffuse-type GC in Ardabil. Similar to our study, the prevalence of positive MN-FH (malignant neoplasm family history) was not associated to any of the clinicopathologic features (i.e. sex, age, and histologic subtypes) (22). Case–control studies have mostly shown that the family history association was not significant in CGC but meaningful in NCGC (23, 24). Distal gastric adenocarcinoma risk associated positively with GC family history (OR, 2.15), especially early-onset (<50 yr) GC (OR, 2.82) (25). Moreover, Song et al. reported a relationship between GC family history and the risk of GC in NCGC (HR, 1.83), but not in CGC (21). In another study, a family history of precancerous lesions and GC was associated with a 2.5-fold and a 3.8-fold increase in non-cardia GC hazard, respectively (26).

We did not find any significant association of GC family history in first-degree relatives with the risk of GC. Moreover, increasing the number of affected first-degree relatives did not significantly increase the risk of GC overall. In this high-risk area of CGC in West Asia, the overall rate of GC family history is almost the same in GC patients and controls. However, a significant association was found between GC risk and a family history of GC in siblings compared to parents. The risk was greatly increased when two or more brothers were affected. Determining the type of first-degree relatives with GC may be more important than assessing family history alone for predicting the risk of GC in Ardabil. We did not find a familial tendency to CGC and non-CGC as well as histopathologic features. The results also did not change after adjusting *P*-values using *Bonferroni's correction*, altering the *P*-values to more stringent values (data not shown).

Like other studies, one of the limitations of our study was that family history was based on self-report through questionnaires and it was impracticable to validate reported cancers. In addition, because family history information was collected only once during the study, other family members may be diagnosed with GC during the follow-up period, leading to an underestimation of prevalence of the family history of cancer.

Conclusion

Heterogeneity among studies suggests various genetic predispositions and etiologies. GC in people with a family history may provide useful data regarding molecular genetic pathways contributing to sporadic cancers and might improve our perception of GC. Familial aggregation might be the result of a combination of a shared environment, inherited genetic susceptibility, and common behaviors. It has shown no specific single nucleotide polymorphism (SNP) to correlate with GC familial clustering. Genome-wide association studies (GWAS) may classify GC in individuals with a family history based on genetic markers compared with the morphology and family history, which may enhance our perception of gastric carcinogenesis. Therefore, specification of inherited factors in individuals with GC family history is an important crucial step for early disease management and diagnosis. These factors may be different between low-risk areas compared to high-risk areas. A long-term prospective study can provide stronger evidence of an association between the type of first-degree relatives with GC and the risk of increased GC in this high-risk area.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interest.

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