RESEARCH COMMUNICATION

# Family History of Cancer and Risk of Gastric Cancer in Iran

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## Abstract

**Introduction: Gastric cancer is one of the major causes of cancer related death in the world. A number of risk factors are now known to be related to the development of the disease. Previous reports indicated that a family history is a serious risk, but there is a little information about this in Iran. The aim of this study was to explore the relation between family history of cancer in first and second degree relatives and the risk of GC in Iran. Methods: The present study was designed as unmatched case control study. Cases were 746 patients with histologically confirmed GC and the 746 controls were randomly selected among the healthy participants in a health survey. Family history was extracted from a standard history form completed by the patient or from records created by a health care provider. Mantel-Heanszel odds ratios were computed for removing the confounding effect of age and sex. Results: Overall, 9.7% of cases versus 5.6% of controls reported a family history of GC. Risk increased over twofold for this group. There was no significant association among family history of other cancers and GC (P>0.05). Conclusion: In conclusion, this study showed that family history of GC, especially in first-degree relatives, increases the risk of development of the disease. Further studies are needed to better understand the roles of genetic and environmental factors and their interaction in gastric cancer development in the Iranian community.**

**Keywords:** Gastric cancer - family history - first degree relatives - case-control study

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## Introduction

Gastric cancer (GC) is one of the major causes of cancer related death in the world, even though its incidence has decreased over the past decade (Pourhoseingholi et al., 2007; Moghimi-Dehkordi et al., 2008) GC is the most common malignancy after lung cancer in Iran. In recent years, cancer morbidity and mortality increased in Iran, and GC is ordered second among all cancers in this country(Safaee et al., 2009).

A number of environmental factors are now known to be related to the development of the disease(Yatsuya et al., 2002). Smoking, alcohol consumption, Helicobacter pylori infection, and dietary habits have been stressed as important risk factors, but recently the genetic nature of gastric adenocarcinoma have received much attention (Bernini et al., 2006).

Previous reports from various study have indicated that family history is a serious risk for gastric cancer (Inoue et al., 1998). Most epidemiologic studies reported a risk of gastric cancer between 1.5 and 3.5 for subjects with relatives with gastric cancer. This may be partly due to the fact that relatives tend to be exposed to the same environmental risk factors, but also to inheritable (genetic) susceptibility (Foschi et al., 2008).

Although GC is one of the most common cancers in Iran, nonetheless, only a limited number of studies have analyzed possible correlations between family history of cancer and risk of gastric cancer (Yaghoobi et al., 2004). Thus, to provide further data on the issue, we designed a case-control study to explore the relation between family history of cancer in first and second degree relatives and the risk of GC.

## Materials and Methods

This study was designed as unmatched case-control study to assess the impact of a family history (FH) of first and second degree relative with cancer on patients with gastric cancer.

Cases were 746 patients that histologically confirmed gastric cancer , with no previous diagnosis of any cancer and registered in cancer registry center of Research Center for Gastroenterology and Liver Disease(RCGLD), Shahid Beheshti University of Medical Science; Tehran, Iran. This center is a referral center for GI cancer and patients referred to this cancer registry from public and private hospitals. 746 controls were randomly selected among the healthy participants in a health survey conducted by the Department of Health System Research of RCGLD (Barzkar et al., 2009, Pourhoseingholi et al., 2009) in that a total of 5,500 subjects aged≥15 years were invited to participate in an interview about the occurrence of gastric cancer in their first- or second-degree relatives.

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**Table 1. Associations Between Several Aspects of Family History of Cancer and Risk of GC**

| | Cases N (%) | Controls N (%) | ORMH (CI 95%) |
|---|---|---|---|
| Family history of Cancer | | | |
| FDR/SDR | | | |
| No | 570(76.4) | 537(72.0) | 1.01(0.77-1.33) |
| Yes | 176(23.6) | 209(28.0) | |
| FDR* | | | |
| No | 629(84.3) | 644(86.3) | 1.09(0.78-1.54) |
| Yes | 117(15.7) | 102(13.7) | |
| SDR** | | | |
| No | 675(90.5) | 632(84.7) | 1.00(0.69-1.45) |
| Yes | 71(9.5) | 114(15.3) | |
| Family History of Gastric Cancer | | | |
| FDR/SDR | | | |
| No | 674(90.3) | 704(94.4) | 2.12(1.27-3.28) |
| Yes | 72(9.7) | 42(5.6) | |
| FDR* | | | |
| No | 693(92.9) | 728(97.6) | 3.32(1.67-6.41) |
| Yes | 53(7.1) | 18(2.4) | |
| SDR** | | | |
| No | 718(96.2) | 721(96.6) | 1.55(0.78-2.91) |
| Yes | 28(3.8) | 25(3.4) | |
| Family History of Other Cancer | | | |
| FDR/SDR | | | |
| No | 640(85.8) | 570(76.4) | 0.68(0.5-1.03) |
| Yes | 106(14.2) | 176(23.6) | |
| FDR* | | | |
| No | 675(90.5) | 660(88.5) | 0.72(0.48-1.06) |
| Yes | 71(9.5) | 86(11.5) | |
| SDR** | | | |
| No | 698(93.6) | 650(87.1) | 0.85(0.55-1.31) |
| Yes | 48(6.4) | 96(12.9) | |

Detailed information was collected for all first and second degree relatives of cases and controls. Positive family history was defined when the case had at least one first (mother, father, children or sibling) or second degree relative (grand father or mother, aunt and uncle) diagnosed with any malignancy. 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 odds ratio for the association between GC risk and family history of cancer and its 95% confidence intervals were calculated by Mantel-Haenszel summary estimates, organizing the data stratified by sex and age groups (<50, ≥50) into 4 strata. All tests were two sided, with statistical significance attributes to $p<0.05$. Statistical analysis was performed with SPSS (version 13.0) and EPI Info software. Details of the study protocol have been published elsewhere (Safaee et al., 2010).

## Results

A total of 746 patients with GC and 746 healthy controls were analyzed. By design, the proportion of men was higher in cases than in controls, and the age distribution was higher in cases ($p<0.05$).

From the subjects under study, 176 cases (23.6%) and 209 controls (28%) had a family history of any cancer in the first or second degree relatives, of whom 72 and 42 had a family history of GC, respectively. The association between family history of any cancer and the risk of GC is presented in Table 1. No excess risk for gastric cancer was found with a family history of cancer.

Also, Table1 presents the relation between GC risk and several aspects of family history of gastric cancer. Overall, 9.7% of cases versus 5.6% of controls reported a family history of gastric cancer. GC risk increased over twofold for subjects reporting a family with GC. Overall, when the subject had at least one first-degree relative with history of gastric cancer, the odds ratio (OR) was 3.32 (95% CI: 1.67-6.41).

Further analysis showed that there in no statistical association among FH of other cancers and GC ($P>0.05$) (Table 1).

## Discussion

In this case-control study we investigate the effect of several aspect of FH of cancer on GC risk. Our findings confirm that a FH of GC in family, especially in first-degree relatives, increases the risk of GC. Individuals with at least one FDR of GC have a three times increased risk for GC comparing to healthy controls. A positive association among FH and GC and increased risk ranged between 2-5 fold has been reported in many studies(La Vecchia et al., 1992; Kato et al., 1992; Palli et al., 1994; Nagase et al., 1996; Kikuchi et al., 1996; Inoue et al., 1998). Since the family members share a common life style and environment, familial risk for GC doesn't necessarily due to the effect of hereditary factors(Foschi et al., 2008). While several studies have reported that environmental factors like Helicobacter pylori infection may play a more important role than genetic factors in GC development(Ignasi Elizalde and Pique, 2006; Brenner et al., 2009) some studies haven't found a strong correlation between FH of GC and environmental factors, such as lifestyles(Huang et al., 2000).

Some studies(Lissowska et al., 1999; Hemminki et al., 2007; Foschi et al., 2008) not all (La Vecchia et al., 1992; Inoue et al., 1998; Chen et al., 2004) have found that cases with a sibling affected compared to cases with a parent affected having the higher familial risk for GC. In this study we didn't get the information about the different kind of relatives of participants. It is reported that women have a higher familial risk for GC than men (Kikuchi et al., 1996; Ikeguchi et al., 2001; Yatsuya et al., 2002; Hemminki et al., 2007) whereas in some studies (Lissowska et al., 1999; Foschi et al., 2008) there is no difference emerged with the gender of the affected relative. Because of adjustment of odds ratio according to age and sex in the statistical analysis by Mantel-Haenszel method, the crude affect of these variable couldn't be investigate.

In another part of this study, we investigate the correlation between the FH of any cancer and FH of other cancers (except GC) with GC. There is no statistical significance regarding to several aspects of family history such as; FDR and SDR, FDR alone and SDR alone among cases and healthy controls. This result in agreement with another Italian study (Foschi et al., 2008). Bernini el

al.(2006) reported that gastric, colorectal, breast; lung and liver cancer are the most prevalent associated cancers in FDR of their GC patients, respectively. The overall ranking of FH of cancer (except GC) in GC probands varied from country to country. For instance, colorectal, breast, and lung cancer were prevalent in an Italian study (Roviello et al., 2007), lung/larynx cancer, gastrointestinal cancer, and leukemia/lymphoma were most frequent in a Turkey study (Bakir et al., 2003), and colorectal and lung cancer were most common in a report from Taiwan (Chen et al., 2004). It seems that, the more frequent tumors were probably the most prevalent ones occurring in that general population. This difference may be due to this fact that our study is questionnaire based and information on FH is self-reported. It is possible that cases of GC may tend to recall a family history of gastric or other cancers more accurately than controls. It was not possible to evaluate the accuracy of self-reported family histories in this study. Although, studies on the accuracy of the self-reported family history suggest that the sensitivity and specificity of self reported FH of cancer is fairly good even in a case-control study, others have shown that the accuracy of self-reporting FH for colorectal cancer is not very good (Mitchell et al., 2004; Murff et al., 2004; Chang et al., 2006).

One of the limitations of our study is that the information was based on questionnaire and self-reporting reports. Therefore, we can't exclude the possible effect of recall bias on the evaluation of risk for GC patients with positive FH of cancer. Selected of cases and controls from the same region have improved the power of this study. Another limitation of our study was that we did not check for *Helicobacter pylori* (HP) antibody among our study population. HP infection has been suggested as a risk factor for antrum cancer in Japanese populations(Inoue et al., 1998). In this study we used hospital-based cases and population-based controls. In order to reduce this potential bias we use the same interviewer for two groups under study.

In conclusion, this Iranian study showed that only FH of GC in family, especially in first-degree relatives, increases the risk of GC. Further studies of GC are needed to better understand the role genetic factors and environmental factors such as dietary, economical, or educational factors and their interaction in GC development in Iranian community.

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## References

Bakir T, Can G, Siviloglu C, Erkul S (2003). Gastric cancer and other organ cancer history in the parents of patients with gastric cancer. *Eur J Cancer Prev,* **12**, 183-9.

Barzkar M, Pourhoseingholi MA, Habibi M, et al (2009). Uninvestigated dyspepsia and its related factors in an Iranian community. *Saudi Med J,* **30**, 397-402.

Bernini M, Barbi S, Roviello F, et al (2006). Family history of gastric cancer: a correlation between epidemiologic findings and clinical data. *Gastric Cancer,* **9**, 9-13.

Brenner H, Rothenbacher D, Arndt V (2009). Epidemiology of stomach cancer. *Methods Mol Biol,* **472**, 467-77.

Chang ET, Smedby KE, Hjalgrim H, Glimelius B, Adami HO (2006). Reliability of self-reported family history of cancer in a large case-control study of lymphoma. *J Natl Cancer Inst,* **98**, 61-8.

Chen MJ, Wu DC, Ko YC,Chiou YY (2004). Personal history and family history as a predictor of gastric cardiac adenocarcinoma risk: a case-control study in Taiwan. *Am J Gastroenterol,* **99**, 1250-7.

Foschi R, Lucenteforte E, Bosetti C, et al (2008). Family history of cancer and stomach cancer risk. *Int J Cancer* **123**, 1429-32.

Hemminki K, Sundquist J, Ji J (2007). Familial risk for gastric carcinoma: an updated study from Sweden. *Br J Cancer* **96**, 1272-7.

Huang XE, Tajima K, Hamajima N, et al (2000). Comparison of lifestyle and risk factors among Japanese with and without gastric cancer family history. *Int J Cancer* **86**, 421-4.

Ignasi Elizalde J, Pique JM (2006). Risk assessment in relatives of gastric cancer patients: hyperproliferation, genetics, and Helicobacter pylori infection. *Eur J Gastroenterol Hepatol,* **18**, 877-9.

Ikeguchi M, Fukuda K, Oka S, et al (2001). Clinicopathological findings in patients with gastric adenocarcinoma with familial aggregation. *Dig Surg,* **18**, 439-43.

Inoue M, Tajima K, Yamamura Y, et al (1998). Family history and subsite of gastric cancer: data from a case-referent study in Japan. *Int J Cancer,* **76**, 801-5.

Kato I, Tominaga S, Matsumoto K (1992). A prospective study of stomach cancer among a rural Japanese population: a 6-year survey. *Jpn J Cancer Res,* **83**, 568-75.

Kikuchi S, Nakajima T, Nishi T, et al (1996). Association between family history and gastric carcinoma among young adults. *Jpn J Cancer Res,* **87**, 332-6.

La Vecchia C, Negri E, Franceschi S, Gentile A (1992). Family history and the risk of stomach and colorectal cancer. *Cancer*, **70**, 50-5.

Lissowska J, Groves FD, Sobin LH, et al (1999). Family history and risk of stomach cancer in Warsaw, Poland. *Eur J Cancer Prev,* **8**, 223-7.

Mitchell RJ, Brewster D, Campbell H, et al (2004). Accuracy of reporting of family history of colorectal cancer. *Gut,* **53**, 291-5.

Moghimi-Dehkordi B, Safaee A, Zali MR (2008). Survival rates and prognosis of gastric cancer using an actuarial life-table method. *Asian Pac J Cancer Prev* **9**, 317-21.

Murff HJ, Spigel DR, Syngal S (2004). Does this patient have a family history of cancer? An evidence-based analysis of the accuracy of family cancer history. *Jama,* **292**, 1480-9.

Nagase H, Ogino K, Yoshida I, et al (1996). Family history-related risk of gastric cancer in Japan: a hospital-based case-control study. *Jpn J Cancer Res,* **87**, 1025-8.

Palli D, Galli M, Caporaso NE, et al (1994). Family history and risk of stomach cancer in Italy. *Cancer Epidemiol Biomarkers Prev,* **3**, 15-8.

Pourhoseingholi MA, Hajizadeh E, Moghimi Dehkordi B, Safaee A, Abadi A (2007). Comparing Cox regression and parametric models for survival of patients with gastric carcinoma. *Asian Pac J Cancer Prev,* **8**, 412-6.

Pourhoseingholi MA, Kaboli SA, Pourhoseingholi A, et al (2009). Obesity and functional constipation; a community-

based study in Iran. *J Gastrointestin Liver Dis,* **18**, 151-5.
Roviello F, Corso G, Pedrazzani C, et al (2007). High incidence of familial gastric cancer in Tuscany, a region in Italy. *Oncology,* **72**, 243-7.
Safaee A, Moghimi-Dehkordi B, Fatemi S, Ghiasi S, Pourhoseingholi M (2009). Clinicopathological features of gastric cancer: a study based on cancer registry data. *Iranian J Cancer Prev,* **2**, 67-70.
Safaee A, Moghimi-Dehkordi B, Pourhoseingholi MA, et al (2010). Risk of colorectal cancer in relatives: a case control study. *Indian J Cancer,* **47**, 27-30.
Yaghoobi M, Rakhshani N, Sadr F, et al (2004). Hereditary risk factors for the development of gastric cancer in younger patients. *BMC Gastroenterol,* **4**, 28.
Yatsuya H, Toyoshima H, Mizoue T, et al (2002). Family history and the risk of stomach cancer death in Japan: differences by age and gender. *Int J Cancer,* **97**, 688-94.