Original article

Family history of gastric cancer: a correlation between epidemiologic findings and clinical data

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Abstract

Background. The pathogenetic mechanisms behind gastric cancer are still unclear. Its familial aggregation, on the other hand, has been very well documented by many epidemiologists. Nonetheless, only a limited number of studies have analyzed possible correlations between demographic and clinical data.
Methods. Between January 1988 and August 2004, 541 patients underwent gastric resection with a curative intent at our department; demographic information, laboratory data, imaging, operative notes, and pathology reports were available for all patients. During 2004 we conducted a series of structured interviews with the surviving patients or their closest relatives regarding oncological family history, limited to first-degree relatives.
Results. Family history could be obtained in 383 patients (70.8%). Gastric cancer was by far the most frequently associated tumor: 21.9% of the overall number of tumors reported in the family histories were gastric cancers. Patients were also subdivided into those having at least one other family member with stomach cancer (71 patients; 18.5%) and those with no relatives affected by gastric cancer (312 patients; 81.5%). No statistically significant differences between the groups were observed regarding the primary tumor location, size, pTNM classification, and ABO or Rh blood types. However, the intestinal histotype was significantly ($P = 0.015$) more frequently represented in individuals with at least one family member affected by gastric cancer compared with those with no relatives with stomach cancer (71.8% vs 55.1%, respectively).
Conclusions. Stomach cancer has a relevant degree of familial aggregation and in our series of patients, this was even more pronounced for the intestinal histotype.

Key words Gastric cancer · Family history · Epidemiology

Introduction

In Western countries, the incidence of gastric cancer has changed dramatically during the past decades; noncardia gastric cancer is decreasing, while the incidence of cardia adenocarcinoma is one of the fastest rising among all neoplasias [1]. Unfortunately, neither the reasons for the change in frequency nor the exact etiology of stomach cancer are clear. Smoking, alcohol consumption, *Helicobacter pylori* infection, and dietary habits have been stressed as important risk factors [2–4], but more recently the genetic aspects of gastric adenocarcinoma have received much attention [5,6].

The etiology of gastric cancer includes two hereditary familial syndromes; namely, hereditary diffuse gastric cancer (HDGC) and hereditary nonpolyposis colon cancer (HNPCC). HDGC is associated with a diffuse histotype and is caused by germline mutations in the *CDH1* gene [7]. HNPCC mainly predisposes to colorectal and endometrial cancer, but is also associated with gastric cancer to a lesser degree. HNPCC originates from germline mutations in either the *MLH1* gene or other genes involved in DNA mismatch repair [8]. Nonetheless, these cancer syndromes comprise a only a very small percentage of gastric neoplasias.

While several studies [9–14] have observed a familial aggregation in gastric cancer, only very few have attempted to correlate clinical features with family history. In the present study, we evaluated the presence of the familial aggregation of gastric cancer and clinicopathological parameters, including blood type.

Patients and methods

Between January 1988 and August 2004, 541 patients with histologically demonstrated adenocarcinoma of the stomach underwent gastric resection with curative intent at the First Department of General Surgery,

University of Verona, Italy. For each patient, demographic information, clinical data (history and physical examination, laboratory findings, and imaging), operative notes, and pathology reports were available in our Department.

During the year 2004, we attempted to obtain the oncological family history of each patient, using structured interviews carried out either in person or by telephone. After a brief explanation of the purpose of the study, verbal consent was requested before starting the questionnaire. The patient or the closest relative, usually the wife or husband, was asked to report the total number of first-degree relatives in the patient's family, their age, and whether anyone in the family had been diagnosed with cancer. The interview was always conducted by the same physician (M.B.).

In the case of a family member having been diagnosed with neoplasia, the site was always queried. All kinds of tumors were considered, including hematologic malignancies. Only biological relatives were included in the analysis. The ages were the current age for living relatives and the age at death for those who had passed away.

Statistical associations between the presence of a family history of gastric cancer and clinicopathological features were assessed by Pearson's χ^2 test for categorical covariates and Wilcoxon's test for continuous variables. A P value less than 0.05 was considered significant. For all calculations, the R statistical software package was used (www.r-project.org).

Results

Patients and family data collection

Of the 541 patients operated on with curative intent, we were able to obtain oncological family history in 383 individuals (70.8%). The mean age of this patient cohort was 65 years (range, 30 to 93 years), with a mean of 7.6 first-degree relatives. There were 247 men (64.5%) and 136 women (35.5%).

Aggregation of cancer in families

The majority of patients (242; 63.2%) had at least one first-degree relative affected by cancer at any site. Among these 242 patients with a positive oncological family history, 146 (60.3%) had one first-degree relative affected by a neoplastic disease, 76 (31.4%) had two first-degree relatives, and 20 (8.3%) had three or more relatives diagnosed with cancer. The different sites involved in first-degree relatives are shown in Table 1. Stomach cancer was by far the most frequent cancer in the families analyzed, representing 21.9% of the associ-

Table 1. Overall ranking of associated tumors in the first-degree relatives of our gastric cancer patients

Rank	Associated cancer	No. of cases	Percentage
1	Stomach	79	21.9%
2	Colon-rectum	40	11.1%
3	Breast	37	10.2%
4	Lung	33	9.1%
5	Liver	25	6.9%
6	Uterus	15	4.2%
7	Brain	14	3.9%
8	Prostate	13	3.6%
9	Larynx	11	3.0%
10	Esophagus	10	2.8%
11	Pancreas	9	2.5%
12	Bone	8	2.2%
13	Bladder	8	2.2%
14	Leukemia	6	1.7%
15	Lymphoma	6	1.7%
16	Kidney	4	1.1%
17	Oral cavity	3	0.8%
18	Cowden	2	0.6%
19	Melanoma	2	0.6%
20	Ovary	2	0.6%
21	Female genitalia	1	0.3%
	Not specified	32	8.9%

ated cancers. In all, there were 63 families with one associated gastric cancer and 8 families with two associated gastric cancers.

Association of family history of gastric cancer with clinicopathological features

We next analyzed the differences between patients with and without a family history of gastric cancer (Tables 2 and 3). There were 312 (81.5%) patients who were negative for a family history of gastric cancer, while 71 (18.5%) patients had a positive family history of gastric cancer. There were no significant differences in demographic data between these two patient groups (Table 2), indicating that any clinical diversities found between the groups could not be attributed to epidemiologic bias. Correlations between relevant clinicopathological parameters, adjusted for confounding factors such as year of resection, age and sex, are shown in Table 3. A statistically significant difference was observed only for the Lauren classification (P = 0.015). Cases in patients with another gastric cancer in the family were mostly of the intestinal histotype (71.8%), while cases in patients without familial aggregation had a lower percentage of the intestinal histotype (55.1%). Thus, 22.8% of intestinal gastric cancers were in patients who had at least one first-degree relative with gastric cancer, while only 12.5% of patients with non-intestinal gastric cancer had a first-degree relative with gastric cancer, leading to a relative risk of 1.7.

Table 2. Demographic features in patient groups with and without a family history of gastric cancer

Parameter	Negative family history (n = 312; 81.5%)	Positive family history (n = 71; 18.5%)	OR (95% CI)	P value
Age (years)	65.2 ± 12.0[a]	67.6 ± 12.5[a]		0.135
Sex F	113 (36.2%)	23 (32.4%)	1	0.638
M	199 (63.8%)	48 (67.6%)	1.2 (0.7–2.1)	
No. of relatives	7.6 ± 2.6[a]	7.9 ± 2.2[a]		0.336
Age of relatives (years)	59.5 ± 19.8[a]	59.9 ± 19.5[a]		0.753

[a] Mean ± SD

Table 3. Comparison of clinical data in patients with negative and positive family histories of gastric cancer

Parameter	Negative family history (n = 312; 81.5%)	Positive family history (n = 71; 18.5%)	OR (95% CI)[a]	P value (χ[b] test)
Lauren classification				
Intestinal	172 (55.1%)	51 (71.8%)	1	0.015
Nonintestinal	140 (44.9%)	20 (28.2%)	0.5 (0.3–0.9)	
Tumor location				
Distal	148 (47.4%)	30 (42.3%)	1	0.69
Middle	80 (25.6%)	23 (32.4%)	1.4 (0.8–2.6)	
Proximal	68 (21.8%)	14 (19.7%)	1.0 (0.5–1.9)	
Linitis plastica	16 (5.1%)	4 (5.6%)	1.2 (0.3–3.5)	
Dimension (mm)	48.2 ± 29.2[b]	49.4 ± 28.8[b]		0.643
Depth of invasion				
pT1	77 (24.7%)	20 (28.2%)	1	0.87
pT2	86 (27.6%)	20 (28.2%)	0.9 (0.4–1.7)	
pT3	109 (34.9%)	24 (33.8%)	0.8 (0.4–1.6)	
pT4	40 (12.8%)	7 (9.9%)	0.7 (0.2–1.7)	
Nodal involvement				
pN0	118 (37.8%)	28 (39.4%)	1	0.8
pN1	97 (31.1%)	18 (25.4%)	0.8 (0.4–1.5)	
pN2	59 (18.9%)	15 (21.1%)	1.1 (0.5–2.2)	
pN3	38 (12.2%)	10 (14.1%)	1.1 (0.5–2.5)	
Distant metastasis				
pM0	276 (88.5%)	66 (93.0%)	1	0.37
pM1	36 (11.5%)	5 (7.0%)	0.5 (0.2–1.3)	
Blood types				
0	142 (45.5%)	30 (42.3%)	1	0.74
A	142 (45.5%)	32 (45.1%)	1.1 (0.6–1.9)	
AB	7 (2.2%)	3 (4.2%)	2.1 (0.4–8.3)	
B	21 (6.7%)	6 (8.5%)	1.3 (0.5–3.5)	
Rh+	266 (85.3%)	61 (85.9%)	1	0.96
Rh−	46 (14.7%)	10 (14.1%)	0.9 (0.4–1.9)	

[a] Age-, sex-, and year of resection-adjusted odds ratios
[b] Mean ± SD

Discussion

One of the most relevant findings of the present study was the significant familial aggregation of gastric cancer even in a relatively small survey. In fact, in an area with a relatively low incidence of stomach cancer, almost one in five patients diagnosed with gastric cancer had at least one first-degree relative affected with the same dismal disease.

While a remarkable familial aggregation has already been reported by epidemiologists in Italy [9–11], we found a slightly higher percentage of affected first-degree relatives than in those studies. Similar percentages have been found in Poland, a high-incidence area [12]. Our findings are also consistent with studies conducted in the United States and Japan [13,14]. As with some other studies, the present study suffers from the limitation of using self-reporting data collection;

interviewing persons without direct medical knowledge may raise a recall bias objection with regards to cases of nonspecified cancer. Nevertheless, because we investigated only first-degree relatives, such a bias is likely to have been limited.

Lung, colon, and prostate cancers show a familial aggregation rate of approximately 7% [15–17], which is rather high for prostate considering that it is aggregated only by male members of a family. However, breast cancer is a well-known "familial" neoplasia, with a familial aggregation rate of 12.3%, according to a very large survey [18]. Once again, such a frequency is considerably high when considering that this neoplasia is present predominantly in females.

One particularly intriguing question is whether the observed familial aggregation is due to genetic or environmental factors. Thus, the question of screening family members of a patient newly diagnosed with gastric cancer arises. At present, the relative contributions of both environmental and genetic factors remain unclear. Even though a large-scale study conducted in Scandinavia on twins did not show a significant genetic component in gastric cancer, in agreement with findings in other types of cancer [19], this is contrast with other similar studies from Japan [20]. Along these lines, single-nucleotide polymorphisms in proinflammatory genes associated with *Helicobacter pylori* infection may be related to the genetic risk of the development of gastric cancer [5,6].

If specific familial risk factors could be identified, gastric cancer screening may be warranted for patients presenting with precise risk factors, while, from a cost-effectiveness point of view, such screening would not be warranted for all newly diagnosed stomach cancer patients.

As known, there are also hereditary syndromes predisposing to gastric cancer; namely, HNPCC and HDGC. We were not able to identify possible candidates for such syndromes among our patients, because we did not use medical charts to further analyze the family histories collected by interviews. We were not able to determine the affected relatives' ages at diagnosis, or the Lauren histotype if they were affected by gastric cancer. In the case of a candidate for these syndromes being identified, a genetic DNA study would be warranted and prophylactic protocols would be made available for the early diagnosis and treatment of patients with genetically confirmed cases.

We found that there was a significant difference in histotype between patients with and without a family history of gastric cancer. In particular, the intestinal type was observed to be present at a higher frequency in patients with a family history of gastric cancer. This is in contrast to the study by Palli et al. [9], which recruited patients from both high- and low-incidence areas. These conflicting results highlight the need for further studies. In our cohort of gastric cancer patients, a patient with the intestinal histotype had nearly twice the probability of having a first-degree relative with the same neoplasia, compared to a patient with a nonintestinal gastric cancer. This might have further implications for eventual familial screening. Tumor locations, dimensions, and pTNM classifications were not significantly different in patients with and without a family history of gastric cancer, and no significant differences were found for genetically determined features such as blood type and Rh factor.

In conclusion, gastric cancer has a striking familial aggregation: almost one out of five patients affected by gastric cancer had at least one first-degree relative also affected by gastric cancer. The intestinal histotype was significantly more frequently represented in patients with a positive family history of gastric cancer, and nearly one in four patients with an intestinal gastric cancer had another member of the family affected. In our opinion, these results should be given further consideration in light of future guidelines for family screening.

References

1. Corley DA, Kubo A. Influence of site classification on cancer incidence rates: an analysis of gastric cardia carcinomas. J Natl Cancer Inst 2004;15;96:1383–7.
2. Sasazuki S, Sasaki S, Tsugane S. Cigarette smoking, alcohol consumption and subsequent gastric cancer risk by subsite and histologic type. Int J Cancer 2002;101:560–6.
3. Kobayashi M, Tsubono Y, Sasazuki S, Sasaki S, Tsugane S. Vegetables, fruit and risk of gastric cancer in Japan: a 10-year follow-up of the JPHC study cohort I. Int J Cancer 2002;102:39–44.
4. Serafini M, Bellocco R, Wolk A, Ekstroem AM. Total antioxidant potential of fruit and vegetables and risk of gastric cancer. Gastroenterology 2002;123:985–91.
5. El-Omar EM, Carrington M, Chow WH, McColl KE, Bream JH, Young HA, et al. Iterleukin-1 polymorphisms associated with increased risk of gastric cancer. Nature 2000;404:398–402.
6. El-Omar EM, Rabkin CS, Gammon MD, Vaughan TL, Risch HA, Schoenberg JB, et al. Increased risk of noncardia gastric cancer associated with proinflammatory cytokine gene polymorphisms. Gastroenterology 2003;124:1193–201.
7. Dunbier A, Guilford P. Hereditary diffuse gastric cancer. Adv Cancer Res 2001;83:55–65.
8. Chung DC, Rustgi AK. The hereditary nonpolyposis colorectal cancer syndrome: genetics and clinical implications. Ann Intern Med 2003;138:560–70.
9. Palli D, Galli M, Caporaso NE, Cipriani F, Decarli A, Saieva C, et al. Family history and risk of stomach cancer in Italy. Cancer Epidemiol, Biomarkers Prev 1994;3:15–8.

10. Zanghieri G, Di Gregorio C, Sacchetti C, Fante R, Sassatelli R, Cannizzo G, et al. Familial occurrence of gastric cancer in the 2-year experience of a population-based registry. Cancer 1990;66: 2047–51.
11. La Vecchia C, Negri E, Franceschi S, Gentile A. Family history and risk of stomach cancer and colorectal cancer. Cancer 1992; 70:50–5.
12. Lissowska J, Groves FD, Sobin LH, Fraumeni JF Jr, Nasierowska-Guttmejer A, Radziszewski J, et al. Family history and risk of stomach cancer in Warsaw, Poland. Eur J Cancer Prev 1999;8:223–7.
13. Dhillon PK, Farrow DC, Vaughan TL, Chow WH, Risch HA, Gammon MD, et al. Family history of cancer and risk of esophageal and gastric cancers in the United States. Int J Cancer 2001; 93:148–52.
14. Nagase H, Ogino K, Yoshida I, Matsuda H, Yoshida M, Nakamura H, et al. Family history-related risk of gastric cancer in Japan: a hospital-based case-control study. Jpn J Cancer Res 1996;87:1025–8.
15. Bromen K, Pohlabeln H, Jahn I, Ahrens W, Joekel KH. Aggregation of lung cancer in families: results from a population-based case-control study in Germany. Am J Epidemiol 2000;152:497–505.
16. Fuchs CS, Giovannucci EL, Colditz GA, Hunter DJ, Speizer FE, Willett WC. A prospective study of family history and the risk of colorectal cancer. New Engl J Med 1994;331:1669–74.
17. Hayes RB, Liff JM, Pottern LM, Greenberg RS, Schoenberg JB, Schwartz AG, et al. Prostate cancer risk in U.S. blacks and whites with a family history of cancer. Int J Cancer 1995;60:361–4.
18. Collaborative Group on Hormonal Factors in Breast Cancer. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58 209 women with breast cancer and 101 986 women without the disease. Lancet 2001;358:1389–99.
19. Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, et al. Environmental and heritable factors in the causation of cancer. New Engl J Med 2000;343:78–85.
20. Matsukura N, Onda M, Tokunaga A, Yoshiyuki T, Shimizu Y, Nishi K, et al. Simultaneous gastric cancer in monozygotic twins. Cancer 1988;62:2430–5.