# Family History and Risk of Stomach Cancer in Italy[1]

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## Abstract

**One thousand sixteen gastric cancer (GC) patients and 1623 population controls, interviewed in a multicentric study in Italy, reported their family history for gastric, esophageal, and colorectal cancer. A significant association was found only with a history of GC in a sibling or in a parent [odds ratio (OR), 2.6 and 1.7, respectively], which persisted after adjusting for potential confounders including nutrient intake. Adjusted GC risk was higher for subjects having an affected mother than an affected father (OR, 2.3 and 1.3) and showed a further increase for subjects reporting both parents (OR, 3.0) or two or more siblings affected with GC (OR, 8.5). The proportion of patients with an affected first-degree relative was higher among females, in the elderly, and in high-risk areas. Among adult siblings of controls and cases, GC prevalence reported at interview was 1 and 2.7%, respectively; a further increase was shown in families with at least one parent affected (1.4 and 5.7%). GC risk associated with a positive family history was greater among residents of low-risk areas where risks were increased about two-fold. Among cases, family history of GC was not related to blood group A or to histological type according to the Lauren classification. These findings are discussed in terms of the contributions of genetic and environmental risk factors and their possible interactions.**

## Introduction

Despite a decreasing trend observed in nearly all countries, gastric cancer is estimated to be the second most common cancer in the world and the second leading cause of cancer death (1, 2). Although several dietary risk factors have been identified, the causative and protective agents for GC[3] remain to be clarified. In Italy, high-risk areas for GC are located in the north-central part of the country, while rates are uniformly low in the southern regions (3). Familial factors have been considered important in GC susceptibility, although it is difficult to distinguish between genetic and environmental exposures shared by family members. Recently, studies in Italy have shown an increased GC risk associated with a positive FH (4, 5), which agrees with reports from several other countries (6, 7).

In a large multicenter case-control study of GC, we found that intake of certain dietary items and nutrients influence the risk of GC and its geographic variation (8, 9). Herein we present results from further analyses which quantify the effect of family history on GC risk.

## Subjects and Methods

Details of the study protocol have been published elsewhere (8). Briefly, all incident cases of GC with histological confirmation were identified, along with a random sample of the resident population of 4 areas in Italy, 2 of which were high risk (1: Forli', Cremona, Imola; 2: Florence, Siena) and 2 of which were low risk (3: Genoa; 4: Cagliari) for GC.

Trained interviewers questioned 1016 GC patients aged 75 years or less (640 males, 376 females) who were first diagnosed between June 1985 and December 1987 among residents in the study areas, and 1623 (959 males, 664 females) controls randomly selected from comparable sex and age strata of the same population. The questionnaire recorded demographic, socioeconomic, residential, occupational, smoking, medical, family, and dietary information.

Detailed information was collected for all first degree relatives of cases and controls. Interviewers first asked questions about the number and sex distribution of all siblings who had reached 20 years of age. Parents and siblings affected with gastric, esophageal, and colorectal cancer were investigated. No information was available on age at diagnosis for the relatives reported as affected with any cancer; the sex of affected siblings was not coded.

Adjusted OR estimates for the association between GC risk and factors under study and corresponding 95% confidence intervals were obtained (10). To account for potential confounding by factors shown to be significantly related to GC (8), multivariate logistic regression analyses were conducted. All the regression models included terms for age (actual age in years), sex, area (4 study areas), place of residence (urban/rural), migration from south (yes/no), socioeconomic status (low, medium, and high, based on a combination of occupation and educational level), and Quetelet index (tertile categories of weight/height squared). The intakes of two nutrients, identified as most relevant in the previous analysis, were included in the logistic regression models as absolute levels (log-scale), together with total calories (log-scale) to adjust for total energy intake. To evaluate the effect of FH, categorical variables were included in the regression models, separately or simultaneously. Analyses

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[3] The abbreviations used are: GC, gastric cancer; FH, family history; OR, odds ratio.

*Table 1* Distribution of cases and controls according to familial (overall by sex and by number of affected relatives), parental, and sibling GC history. Adjusted ORs and 95% CI (Italian study, 1985–1988)

| GC family history | No. of Cases (%) | No. of controls (%) | Adjusted OR (CI)[a] |
|---|---|---|---|
| Overall FH[b] | | | |
| Negative | 803 | 1446 | 1.0 |
| Positive | 213 (21.0) | 177 (10.9) | 2.0 (1.6–2.5) |
| Males | | | |
| Negative | 519 | 860 | 1.0 |
| Positive | 121 (18.9) | 99 (10.3) | 1.8 (1.3–2.4) |
| Females | | | |
| Negative | 284 | 586 | 1.0 |
| Positive | 92 (24.5) | 78 (11.7) | 2.2 (1.5–3.2) |
| Parental history | | | |
| Negative | 868 | 1487 | 1.0 |
| Positive | 148 (14.6) | 136 (8.4) | 1.7 (1.3–2.2) |
| Sibling history | | | |
| Negative | 925 | 1576 | 1.0 |
| Positive | 91 (9.0) | 47 (2.9) | 2.6 (1.8–3.7) |
| No. of first-degree relatives | | | |
| None | 803 | 1446 | 1.0 |
| 1 | 163 (16.0) | 163 (10.0) | 1.7 (1.3–2.1) |
| 2+ | 50 (4.9) | 14 (0.8) | 5.5 (3.0–10.2) |
| Total | 1016 | 1623 | |

[a] CI, confidence interval.
[b] Any first-degree relative.

*Table 2* Distribution of cases and adjusted controls according to sex and parental history for GC; ORs and 95% CI (Italian study, 1985–1988)[a]

| | Parents with gastric cancer | | | | |
|---|---|---|---|---|---|
| | None | Father | Mother | Both | Total |
| Cases | | | | | |
| Males | 555 (86.7) | 43 (6.7) | 33 (5.2) | 9 (1.4) | 640 (100) |
| Females | 313 (83.2) | 30 (8.0) | 29 (7.7) | 4 (1.1) | 376 (100) |
| Total | 868 (85.4) | 73 (7.2) | 62 (6.1) | 13 (1.3) | 1016 (100) |
| Controls | | | | | |
| Males | 883 (92.1) | 47 (4.9) | 27 (2.8) | 2 (0.2) | 959 (100) |
| Females | 604 (91.0) | 38 (5.7) | 18 (2.7) | 4 (0.6) | 664 (100) |
| Total | 1487 (91.6) | 85 (5.2) | 45 (2.8) | 6 (0.4) | 1623 (100) |
| Adjusted OR | 1.0 | 1.3 (1.0–2.0) | 2.3 (1.5–3.5) | 3.0 (1.8–8.7) | |

[a] Logistic model including terms for sex, age, study area, residence, migration social class, body mass index, GC history in siblings, and nutrient intake (total energy intake, protein, vitamin C). CI, confidence interval.

*Table 3* Distribution of cases and controls according to sex and number of siblings affected by GC; adjusted ORs and 95% confidence interval (Italian study, 1985–1988)

| | No. of siblings with gastric cancer | | | |
|---|---|---|---|---|
| | 0 | 1 | 2+ | Total |
| Cases | | | | |
| Males | 589 (92.0) | 39 (6.1) | 12 (1.9) | 640 (100) |
| Females | 336 (89.3) | 33 (8.8) | 7 (1.9) | 376 (100) |
| Total | 925 (91.0) | 72 (7.1) | 19 (1.9) | 1016 (100) |
| Controls | | | | |
| Males | 933 (97.3) | 25 (2.6) | 1 (0.1) | 959 (100) |
| Females | 643 (96.8) | 19 (2.9) | 2 (0.3) | 664 (100) |
| Total | 1576 (97.1) | 44 (2.7) | 3 (0.2) | 1623 (100) |
| Adjusted OR[a] | 1.0 | 2.2 (1.4–3.2) | 8.5 (2.4–29.4) | |

[a] Logistic model including terms for sex, age, study area, residence, migration social class, body mass index, GC history in parents, and nutrient intake (total energy intake, protein, vitamin C).

were also carried out separately for women and men, and for high-risk and low-risk areas.

For two variables with information available only for cases (blood group and Lauren histological type), the association with FH was studied with a model using FH as a dependent variable (any relative affected, yes/no), while the confounders and the variables of interest were considered as independent.

## Results

Table 1 shows the distribution of cases and controls according to FH and type and number of affected relatives. GC risk increased two-fold for subjects reporting any first degree relative with GC and was higher when a sibling was affected. Having two or more affected relatives was associated with a further elevation in GC risk (OR, 5.5). The risk associated with GC occurrence in any first degree relative tended to be slightly greater for women than men (OR, 2.2 and 1.8).

GC risk was higher for subjects reporting an affected mother rather than an affected father (OR, 2.3 and 1.3, respectively) and was further increased for those reporting both parents affected (OR, 3.0) (Table 2). Overall, however, more fathers than mothers were reported with GC by both cases (86 *versus* 75) and controls (91 *versus* 51). When considered separately, females tended to show higher familial GC risks than males, especially when the mother was affected (OR, 3.2 and 1.7, respectively), while the risks for females and males were similar when the father was affected (OR, 1.4 and 1.3, respectively).

Table 3 shows the distribution of cases and controls according to number of siblings with GC. The risk was increased with one affected sibling but rose further when two or more were affected (OR, 2.2 and 8.5, respectively). Females again had a higher risk than males when one sibling was affected (OR, 2.4 and 2.0, respectively). No significant interaction was found between parental and sibling history for GC. Subjects reporting both a parent and a sibling with GC were at increased risk (OR, 4.4) but not as much as those reporting two affected siblings.

*Table 4* Prevalence of GC among adult siblings of cases and controls according to sex and age at diagnosis for cases and age at interview for controls

| Age at diagnosis (yr) | Males | | | | | Females | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *n* | With GC affected siblings | No. of siblings | Siblings with GC | GC prevalence among siblings (%) | *n* | With GC affected siblings | No. of siblings | Siblings with GC | GC prevalence among siblings (%) |
| Cases | | | | | | | | | | |
| 30–39 | 11 | – | 29 | – | – | 7 | – | 25 | – | – |
| 40–49 | 52 | 2 | 119 | 3 | 2.5 | 30 | – | 56 | – | – |
| 50–59 | 136 | 7 | 446 | 9 | 2.0 | 61 | 3 | 236 | 3 | 1.3 |
| 60–69 | 238 | 24 | 815 | 30 | 3.7 | 141 | 20 | 534 | 25 | 4.7 |
| 70–75 | 203 | 18 | 726 | 23 | 3.2 | 137 | 17 | 515 | 20 | 3.9 |
| TOTAL | 640 | 51 | 2135 | 65 | 3.0 | 376 | 40 | 1366 | 48 | 3.5 |
| Controls | | | | | | | | | | |
| 30–39 | 46 | – | 104 | – | – | 42 | – | 75 | – | – |
| 40–49 | 133 | 1 | 339 | 1 | 0.3 | 111 | – | 243 | – | – |
| 50–59 | 203 | 5 | 601 | 5 | 0.8 | 135 | 2 | 419 | 2 | 0.5 |
| 60–69 | 308 | 5 | 1055 | 5 | 0.5 | 205 | 8 | 726 | 8 | 1.1 |
| 70–75 | 269 | 15 | 896 | 16 | 1.8 | 171 | 11 | 568 | 13 | 2.3 |
| TOTAL | 959 | 26 | 2995 | 27 | 0.9 | 664 | 21 | 2031 | 23 | 1.1 |

*Table 5* Proportion of cases and controls reporting any first-degree relative, a parent, or a sibling affected with GC by study area (high *versus* low GC risk)

| | % of Cases | % of Controls | Adjusted OR[a] |
|---|---|---|---|
| Familial history | | | |
| High GC risk area[b] | 23.9 | 13.7 | 1.8 |
| Low GC risk area[c] | 9.3 | 2.8 | 3.7 |
| Parental history | | | |
| High GC risk area | 16.6 | 10.5 | 1.6 |
| Low GC risk area | 6.4 | 2.2 | 3.3 |
| Sibling history | | | |
| High GC risk area | 10.2 | 3.6 | 2.4 |
| Low GC risk area | 3.9 | 0.7 | 4.4 |

[a] Positive *vs.* negative FH.
[b] Florence/Siena and Forli'/Imola.
[c] Genoa, Cagliari.

*Table 6* Distribution of 954 GC cases according to blood group[a] and family GC history

| | Blood group[b] | | | | Total |
|---|---|---|---|---|---|
| | O | A | B | AB | |
| Positive | 75 (19.3)[c] | 95 (22.0) | 20 (20.6) | 8 (22.2) | 198 (20.8) |
| Negative | 314 (80.7) | 337 (78.0) | 77 (79.4) | 28 (77.8) | 756 (79.2) |
| Total | 389 (100) | 432 (100) | 97 (100) | 36 (100) | 954 (100) |
| Adjusted OR | 1.0 | 1.1 (0.7–1.5)[d] | 1.0 (0.6–1.8) | 1.1 (0.5–2.5) | |

[a] Any first-degree relative.
[b] Blood group was not available for 62 cases.
[c] Numbers in parentheses, %.
[d] Confidence intervals.

Overall, adjusted ORs obtained by multivariate logistic models for family, parental, or sibling GC history were not substantially modified by inclusion of terms for confounders and intake of nutrients.

Table 4 shows the crude prevalence of GC in 5026 siblings (2495 sisters and 2531 brothers) of 1623 population controls and in 3501 siblings (1747 sisters and 1754 brothers) of 1016 GC cases interviewed in the study, by age at interview and sex. Sex distribution among siblings according to the sex of the interviewed subjects was well balanced. The GC prevalence among adult siblings increased with age and was higher for cases than controls and for females than males (3.5 *versus* 3.0% for female and male cases, and 1.1 *versus* 0.9% for controls). Prevalence of GC among siblings of cases and controls also varied considerably according to parental GC history (2.7 and 1.0%, respectively, when no parent was affected with GC; 5.8 and 1.4%, respectively, when at least one parent was affected).

A higher proportion of female GC cases reported at least one sibling with GC, compared to male cases (10.6 *versus* 8.0%). In both sexes the proportion of cases and controls with affected siblings rose with increasing age. However, for cases a peak was shown between 60 and 69 years (10.1 and 14.2% for males and females, respectively), while for controls the peak was at 70–75 years of age (5.7 and 6.4%, respectively).

The proportion of cases and controls reporting GC in any first degree relative varied markedly according to study area (Table 5). A positive FH was reported by 23.9 and 9.3% among cases (and 13.7 and 2.8% among controls) in high-risk and low-risk areas, respectively. The five-fold difference in FH between population controls in high *versus* low-risk areas was larger than the differences between cases and controls within each study area. The case-control differences were greater in low-risk areas, where FH prevalence showed a 3-fold variation. The familial ORs were consistently increased (around 100%) in low-risk areas in comparison to high-risk areas.

Table 6 shows the distribution of 954 GC cases according to FH and blood group. The prevalence of FH was somewhat higher among cases with blood group A, but the association almost disappeared after adjusting for other variables. Lauren histological type was available for 923 GC cases reclassified by one pathologist; its distribution by FH showed a nonsignificant association with the mixed-unclassified types (OR, 1.3). No excess risk for GC was found with a FH of esophageal or colorectal cancers.

## Discussion

This large population-based study in Italy revealed an increased GC risk associated with a positive FH of GC but not esophageal or colorectal cancers. GC risk was especially high when a mother or sibling was affected but most notably when two or more first-degree relatives were affected. We also found that the familial risk of GC was higher for female subjects. This might be explained by gender differences in the ability to report FH with women generally being more reliable. This study, however, focused on first-degree relatives, so that relevant misclassification seems unlikely. The reason for higher risks when the maternal line was involved is unclear, but it seems unlikely to be due to differences in reporting or diagnosis. Lifestyle factors may contribute to the familial pattern, since maternal dietary practices strongly affect the dieting habits and nutritional status of the offspring. The higher risk associated with GC-affected mothers is consistent with a previous study showing a maternal inheritance pattern for chronic atrophic gastritis, an established precursor lesion for GC (11). A characteristic feature of GC in all countries and time periods is the male predominance, presumably due to environmental factors (2, 12), so FH might be more easily detected among female cases as seen in this study. We also found that the familial risks were higher in low- *versus* high-risk areas, suggesting that genetic factors may be more apparent in populations at low GC risk. It seems likely that both genetic and environmental factors play a role in gastric carcinogenesis (7, 13) and contribute to the familial tendency that we and others have observed. Of course, random occurrence of a relatively common event in a group of related individuals must be taken into account, particularly in the high-risk study areas, where the cumulative risks of GC are estimated to be higher than 4 and 2% for males and females, respectively (14). A limitation of our study was that information was not available on the sex and age at diagnosis of GC among the affecting siblings. Overall the sex distribution of the two sibling series was well balanced and their age distribution can be considered on average similar to that of interviewed subjects. As expected on the basis of age-specific GC incidence rates, controls showed a peak in GC prevalence among their siblings in the oldest age group. In contrast, among the siblings of cases this peak appeared earlier, suggesting an earlier age distribution of familial cases. However, the younger onset of familial GC is not so evident as for other cancer sites, notably breast cancer for which a clear inheritance pattern has been identified for premenopausal cases with bilateral tumors (15, 16). Familial susceptibility to GC has been linked to the Lauren diffuse type and to blood group A (17), but our study failed to confirm these associations (18). Further studies of GC including biomarkers are needed to better understand the mechanisms of familial susceptibility, including genetic and environmental interactions.

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## References

1. Parkin, D. M., Pisani, P., and Ferlay, J. Estimates of the worldwide incidence of eighteen major cancers in 1985. Int. J. Cancer, *54*:594–606, 1993.

2. Kurihara, M., Aoki, K., and Tominaga, S. Cancer Mortality Statistics in the World. Nagoya: Univ. Nagoya Press, 1984.

3. Parkin, D. M., Muir, C. S., Whelan, S. L., Gao, J-T., Ferlay, J., and Powell, J. (eds.). Cancer Incidence in Five Continents, Vol. VI (IARC Scientific Pub. No. 120). Lyon, France: International Agency for Research on Cancer, 1992.

4. Zanghieri, G., Di Gregorio, C., Sassatelli, R., Cannizzaro, G., Carriero, A., and Ponz De Leon, M. Familial occurrence of gastric cancer in the 2-year experience of a population-based registry. Cancer (Phila.), *66:* 2047–2051, 1990.

5. La Vecchia, C., Negri, E., Franceschi, S., and Gentile, A. Family history and the risk of stomach and colorectal cancer. Cancer (Phila.), *70:* 50–55, 1992.

6. Graham, S., and Lilienfeld, D. M. Genetic studies of gastric cancer in humans: an appraisal. Cancer (Phila.), *11:* 945–958, 1958.

7. Albert, S., and Child, M. Familial cancer in the general population, Cancer (Phila.), *40:* 1674–1679, 1977.

8. Buiatti, E., Palli, D., Decarli, A., Amadori, D., Avellini, C., Bianchi, S., Biserni, R., Cipriani, F., Cocco, P., Giacosa, A., Marubini, E., Puntoni, R., Vindigni, C., Fraumeni, J. F., Jr., and Blot, W. J. A case-control study of gastric cancer and diet in Italy. Int. J. Cancer, *44:* 611–616, 1989.

9. Buiatti, E., Palli, D., Decarli, A., Amadori, D., Avellini, C., Bianchi, S., Bonaguri, C., Cipriani, F., Cocco, P., Giacosa, A., Marubini, E., Minacci, C., Puntoni, R., Russo, A., Vindigni, C., Fraumeni, J. F., Jr., and Blot, W. J. A case-control study of gastric cancer and diet in Italy: II. Association with nutrients. Int. J. Cancer, *45:* 896–901, 1990.

10. Breslow, N. E., and Day, N. E. Statistical Methods in Cancer Research, Vol. I. The Analysis of Case-Control Studies (IARC Scientific Publ. 32). Lyon, France: International Agency for Research on Cancer, 1980.

11. Bonney, G. E., Elston, R. C., Correa, P., Haenszel, W., Zavala, D. E., Zarama, G., Collazos, T., and Cuello, C. Genetic association of gastric carcinoma: I. Chronic atrophic gastritis. Genet. Epidemiol., *3:* 213–224, 1986.

12. Sandler, S. R., and Holland, K. L. Trend and gastric cancer sex ratio in the United States. Cancer (Phila.), *59:* 1032–1035, 1987.

13. Miller, A. B. Risk factors from geographic epidemiology for gastrointestinal cancer. Cancer (Phila.), *50:* 2533–2540, 1982.

14. Biggeri, A., and Buiatti, E. I Tumori dello Stomaco. *In:* R. I. Zanetti and P. Crosignani (eds.), Il Cancro in Italia. I Dati di Incidenza dei Registri Tumori 1983–1987, pp. 145–148. Torino: Lega Italiana per la Lotta contro i Tumori and Associazione Italiana di Epidemiologia, 1992.

15. William, W. R., and Anderson, D. E. Genetic epidemiology of breast cancer: segregation analysis of 200 Danish pedigrees. Genet. Epidemiol., *1:* 7–20, 1984.

16. Claus, E. R., Risch, N. J., and Thompson, W. D. Genetic analysis of breast cancer in the cancer and steroid hormone study. Am. J. Hum. Genet., *48:* 232–242, 1991.

17. Nomura, A. Stomach. *In:* D. Schottenfeld and F. Fraumeni, Jr., Cancer Epidemiology and Prevention, pp. 624–637. Philadelphia: W. B. Saunders, 1982.

18. Buiatti, E., Palli, D., Bianchi, S., Decarli, A., Amadori, D., Avellini, C., Cipriani, F., Cocco, P., Giacosa, A., Lorenzini, L., Marubini, E., Puntoni, R., Saragoni, A., Fraumeni, J. F., Jr., and Blot, W. J. A case-control study of gastric cancer and diet in Italy. III. Risk patterns by histologic type. Int. J. Cancer, *48:* 369–374, 1991.