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# Partial gastrectomy and subsequent gastric cancer risk

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**Abstract**

***Study objective*—The aim was to analyse the relationship between partial gastrectomy and gastric cancer risk.**

***Design*—This was a case control study, using a structured questionnaire to obtain problem orientated medical history and sociodemographic data.**

***Setting*—The study was conducted in a network of hospitals in the Greater Milan area between January 1985 and February 1990.**

***Subjects*—Subjects were 563 incident cases of histologically confirmed gastric carcinoma (347 males, 216 females, median age 60 years, range 28 to 74) and 1501 controls (885 males, 626 females, median age 58 years, range 23 to 74) in hospital for acute, non-neoplastic, non-digestive-tract disorders. Less than 3% of cases or controls refused to be interviewed.**

***Measurements and main results*—Relative risks (RR) and the corresponding 95% confidence intervals (CI) were determined, adjusted for age and sex plus area of residence, education, and smoking when specified. Within 20 years after gastrectomy, the relative risk of gastric cancer was not significantly raised (RR = 1·2, 95% CI 0·5–2·8), but a positive association emerged after longer time intervals. The RR was 1·6 (95% CI 0·7–4·1) after 20 to 29 years, and 3·5 (95% CI 1·3–10·0) after 30 years or more. These results were consistent in the two sexes and in the subsequent age groups, and not materially influenced by allowance for a number of identified potential confounding factors using multivariate analysis.**

***Conclusions*—The risk of gastric cancer is increased in the long term (20 years or more) after gastrectomy. This is explainable in terms of increased intragastric carcinogen formation following gastrectomy, and/or potential similarities in aetiological correlates of gastric ulcer and carcinoma of the stomach.**

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The risk of gastric cancer in patients surgically treated for benign conditions of the stomach has been investigated in several studies, using either a case-control[1 2] or a prospective approach.[3–7] Studies provide evidence that the incidence of gastric carcinoma is not increased during the first 10 to 15 years following partial gastrectomy and several have even suggested that the risk may be decreased.[4 5 7] By contrast, after longer time intervals some studies have found increased gastric cancer rates[3 5 7] although the evidence is not totally consistent.[1 2 8] These apparent discrepancies may, at least in part, be explained in terms of different frequency of benign conditions (gastric *v* duodenal ulcer), and most of all by failure to allow for a sufficiently long latent period in some of the patients.[5]

To provide further quantitative information on the issue, we consider in this article data on gastrectomy from a large case-control study conducted in northern Italy.

## Methods

The data were derived from an ongoing case-control study of stomach cancer, based on a network including major teaching and general hospitals in the greater Milan area. The general design of the study has been described previously.[9]

Briefly, between January 1985 and February 1990, 563 incident cases of histologically confirmed gastric carcinoma (347 males, 216 females, median age 60 years, range 28 to 74) were interviewed. The comparison group consisted of 1501 controls (885 males, 626 females, median age 58 years, range 23 to 74), admitted to the same network of hospitals for a wide spectrum of acute, non-neoplastic, non-digestive-tract conditions (40% traumas, 18% non-traumatic orthopaedic diseases, 27% surgical conditions, 15% various other and miscellaneous illnesses). Less than 3% of subjects identified (cases and controls) refused to be interviewed. The catchment area of cases and controls was comparable: 85% of both cases and controls resided in the same region, Lombardy; 90% of the cases and 93% of the controls came from northern Italy.

A standard questionnaire was used to obtain information on sociodemographic factors, personal characteristics and lifestyle habits, frequency of intake of a few selected indicator foods, and a problem orientated medical history. Age at first diagnosis was specifically elicited for 14 selected diseases or interventions, including gastric ulcer, duodenal ulcer, and gastrectomy.

Statistical analyses were based on standard methods for case-control studies, including sex and age adjusted relative risks (RR) and the corresponding 95% confidence intervals (CI), and estimates from multiple logistic regression models.[10] All the regression equations included terms for age, sex, area of residence, education, and smoking.

## Results

Table I gives the distribution of gastric cancer cases and the comparison group according to sex, age group, education, and smoking. Cases were slightly older than controls, and significantly less educated: compared with subjects with 12 years of education or more, the RR was 1·7 for 7 to 11 years and 2·8 for less than 7 years. No appreciable difference emerged in relation to smoking habits.

The relationship between gastric and duodenal ulcer and subsequent risk of adenocarcinoma of the stomach is considered in table II. Nine percent of the cases versus 4·7% of the controls reported a history of gastric ulcer in the past, giving a RR of 2·0 (95% CI 1·4–2·8). The excess risk was greater in the first five years before stomach cancer diagnosis (RR = 4·6, 95% CI 2·4–8·9), possibly on account of misdiagnosis of some early gastric cancer cases as benign ulcer, and declined towards unity for longer periods before diagnosis: for ulcers diagnosed 10 years or more earlier the RR was 1·3 with 95% CI 0·8 to 2·1. With reference to duodenal ulcer, the proportion of gastric cancer cases with a positive history (6·9%) was similar to that of controls (6·2%), and all the relative risks were close to unity.

Gastrectomy in relation to subsequent gastric cancer risk after different time intervals is considered in table III. Within the first 10 years after gastrectomy, the risk of stomach cancer was not increased (RR = 1·2, 95% CI 0·5–2·8), but a positive association emerged after longer time intervals. After 20 to 29 years, the RR was 1·6, with 95% CI 0·7–4·1, and increased to 3·5 (1·3–10·0) after 30 years or more. The results were not materially influenced by allowance for a number of potential confounding factors using multiple logistic regression.

Table IV analyses the relationship between time since gastrectomy in separate strata of sex and age. In none of the strata considered was a significant association observed within the first 20 years after gastrectomy. For longer delays, the relative risks were increased in both sex and age groups, and, although apparently higher in females and under age 60 years, were not significantly heterogeneous.

*Table I Distribution of 563 cases of gastric cancer and 1501 controls according to sex, age, education and smoking. Milan, Italy 1985–90*

| | Gastric cancer | | Controls | |
|---|---|---|---|---|
| | *No* | *%* | *No* | *%* |
| *Sex* | | | | |
| Males | 347 | 61·6 | 885 | 59·0 |
| Females | 216 | 38·4 | 616 | 41·0 |
| *Age group (years)* | | | | |
| <45 | 54 | 9·6 | 292 | 19·5 |
| 45–54 | 120 | 21·3 | 387 | 25·8 |
| 55–64 | 198 | 35·2 | 469 | 31·2 |
| 65–74 | 191 | 33·9 | 353 | 23·5 |
| *Education (years)* | | | | |
| <7 | 372 | 66·1 | 755 | 50·3 |
| 7–11 | 132 | 23·4 | 428 | 28·5 |
| ⩾12 | 56 | 9·9 | 317 | 21·1 |
| Unknown | 3 | 0·5 | 1 | 0·1 |
| *Tobacco smoking* | | | | |
| Never smokers | 246 | 43·7 | 663 | 44·2 |
| Ex-smokers | 108 | 19·2 | 266 | 17·7 |
| Current smokers | 209 | 37·1 | 572 | 38·1 |

*Table II Distribution of 563 cases of gastric cancer and 1501 controls according to history of gastric and duodenal ulcer. Milan, Italy, 1985–90*

| *Disease* | *Years since diagnosis* | *Gastric cancer* | *Controls* | *Relative risk estimates (95% CI)* *M-H[a]* | *MLR[b]* |
|---|---|---|---|---|---|
| Gastric ulcer | Never | 513 | 1430 | 1[c] | 1[c] |
| | <5 | 19 | 12 | 4·6 (2·4–8·9) | 3·4 (1·4–8·2) |
| | 5–9 | 7 | 13 | 1·5 (0·6–3·9) | 1·5 (0·5–4·4) |
| | ⩾10 | 24 | 46 | 1·3 (0·8–2·1) | 1·3 (0·7–2·1) |
| Duodenal ulcer | Never | 524 | 1407 | 1[c] | 1[c] |
| | <5 | 6 | 14 | 1·1 (0·4–2·9) | 1·0 (0·4–2·6) |
| | 5–9 | 5 | 16 | 0·9 (0·3–2·3) | 0·8 (0·2–2·8) |
| | ⩾10 | 28 | 64 | 1·1 (0·7–1·8) | 1·1 (0·7–1·7) |

[a] Mantel-Haenszel estimates adjusted for age and sex
[b] Estimates from multiple logistic regression equations including terms for age, sex, area of residence, education, and smoking
[c] Reference category
CI = Confidence interval

*Table III Relation of gastric cancer risk with gastrectomy. Milan, Italy, 1985–90*

| *Time since gastrectomy (years)* | *Gastric cancer* | *Controls* | *Relative risk estimates (95% CI)* *M-H[a]* | *MLR[b]* |
|---|---|---|---|---|
| Never | 539 | 1469 | 1[c] | 1[c] |
| <20 | 8 | 16 | 1·2 (0·5–2·8) | 1·2 (0·5–3·0) |
| 20–29 | 7 | 11 | 1·6 (0·7–4·1) | 1·5 (0·5–3·9) |
| ⩾30 | 9 | 5 | 3·5 (1·3–10·0) | 3·3 (1·1–10·1) |
| $\chi^2_1$ (trend) | | | 6·91 (p = 0·01) | 6·31 (p = 0·01) |

[a] Mantel-Haenszel estimates adjusted for age and sex
[b] Estimates from multiple logistic regression equations including terms for age, sex, area of residence, education, and smoking
[c] Reference category
CI = Confidence interval

## Discussion

The findings of this case-control investigation are consistent with the results of two further case-control studies[1 2] and three historical cohort studies[4 5 7] conducted in Britain, Norway, and Iceland, and provide further quantitative evidence of increased gastric cancer incidence several years after gastrectomy. The time pattern of gastric cancer risk following partial gastrectomy (with no excess during the first 20 years approximately) is consistent with most previous work on the topic and suggests that an initial favourable effect, possibly deriving from reduction of the surface of gastric mucosa[4 5] and/or selective removal of abnormal areas during surgical "screening" for gastric cancer, is later substituted by an increased risk.

This gradual increase in gastric cancer risk with increasing time since partial gastrectomy has been seen equally in both sexes and in all different age groups and has been explained in terms of postoperative gastric hypoacidity,[11 12] leading to bacterial overgrowth and possibly production of carcinogens. Some researchers have also found increased levels of N-nitroso compounds[11 12] but the possibility remains that other similarities in aetiological correlates of gastric ulcer and gastric cancer account for the increased risk.[13 14]

Unfortunately, in the present study it has not been possible to collect detailed information on the type of gastric resection performed. Caygill *et al* reported that patients treated with the Bilroth II operation were at higher risk than those treated with Bilroth I and explained this in terms of a carcinogenic effect of bile reflux, which is greater in Bilroth II than in Bilroth I. In other studies,

however, no difference was detected according to type of operation.[5 6]

The case-control design may be inadequate to quantify the risk after gastric ulcer, since subjects with positive history for this condition tend to be at increased gastric cancer risk, independently from gastrectomy. Nonetheless, it is worth noting that the patterns of risk after gastric or duodenal ulcers were not formally heterogeneous.

Although some possibility of recall or selection bias cannot be excluded with such a design, cases and controls came from comparable catchment areas and all digestive tract diagnoses or other conditions potentially related to known or suspected gastric cancer risk factors were explicitly excluded from the comparison group. Furthermore the choice of hospital controls is probably optimal in relation to reliability and comparability of information on diseases and interventions that occurred in the distant past. In fact cases and controls are similarly sensitised towards various aspects of their medical history.[15] With reference to confounding, the results were not appreciably modified by allowance for a number of identified potential distorting factors.

*Table IV Relationship of gastric cancer risk with gastrectomy in separate strata of sex and age. Milan, Italy, 1985–90*

| Time since gastrectomy (years) | Relative risk estimates (95% CI) | | | |
|---|---|---|---|---|
| | Sex | | Age group (years) | |
| | Males | Females | <60 | ≥60 |
| Never | 1[b] | 1[b] | 1[b] | 1[b] |
| <20 | 0·8 (0·3–2·2) | 1·3 (0·1–16·6) | 1·6 (0·5–4·4) | 1·0 (0·3–4·1) |
| ≥20 | 2·0 (0·9–4·4) | 11·2 (1·6–75·6) | 3·3 (1·1–10·1) | 2·0 (0·8–4·6) |

[a] Mantel-Haenszel estimates adjusted for age and (when appropriate) sex
[b] Reference category
CI = Confidence interval

In conclusion, the results of this study can be of interest in terms of aetiological correlates of gastric carcinoma, although their public health implications are now decreased by the substantial decline in gastrectomy as treatment for gastroduodenal ulcer. Further, they should be viewed in comparison with available information on the long term impact on gastric carcinogenesis of treatment with $H_2$ receptor antagonists, which appears, to date, largely reassuring.[16–19]

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