The considerable decline in gastric cancer (GC) incidence and mortality observed for decades in virtually all countries studied suggests that exogenous factors have a central role in gastric carcinogenesis. According to an accepted model, environmental factors are responsible for the evolution of normal mucosa to invasive GC through a continuum of precursor lesions with increasingly regressive phenotype. Although several characteristics of the intraluminal environmental milieu (such as low pH levels, *Helicobacter pylori* infection, bacterial overgrowth, and bile reflux) have been hypothesized to play a role at the beginning of the process, nutritional factors may be important in the chain of events leading to GC. There is evidence to suggest that an increased risk of GC is associated with a dietary pattern characterized by low intake of animal fat and protein, leafy vegetables and fresh fruit, and a high intake of complex carbohydrates, hard grains, salt, nitrites, and irritants. The role played by other food items such as broiled fish, smoked fish and meat, and wine is less certain.

Recent investigations have suggested that time trends of cancer of the gastric cardia reflect, at least in part, a period phenomenon. However, the worldwide recession of GC is mainly attributable to a birth cohort phenomenon. Many descriptive studies have shown a declining incidence or mortality in all cohorts born in the last decades of the 19th century or after 1900. Although a long induction period is an important feature of GC, the secular trends are in accordance with the hypothesis that exposure to aetiological factors early in life is decisive for the development of the disease. More specifically, many migrant studies have suggested that the geographical variation in smoking habits and alcohol intake between birth countries and adoptive countries may account for the observed differences in GC risk.

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**Gastric cancer mortality in the spouses of patients who died from gastric cancer**

**Oriana Nanni, a Giovanna Zoffoli, a Emanuela Scarpi, a Lauro Bucchi, b Paolo Lauriola, c Cesare Cislaghi d and Dino Amadori e**

**Background** There is evidence to support the hypothesis that the main determinants of gastric carcinogenesis act in childhood and adolescence. Based on the assumption that husband and wife share many of these factors (dietary habits and other exogenous exposures) only in adult life, the aim of the study was to demonstrate that the spouses of patients who died from gastric cancer (GC) are not at increased risk of GC death.

**Methods** The study was conducted on data from the province of Forlì (north eastern Italy). The anonymous GC death records provided by the Italian National Statistics Bureau for the years 1969–1988 were matched by month/year of birth, sex, marital status, month/year and place of death with those of the population registries in the area. The subjects identified had a total of 2720 wives or husbands. Gastric cancer mortality observed in the cohort of spouses was compared with that of the general population using the standardized mortality ratio (SMR), calculated by applying the sex-, age-, and time period-specific mortality rate in the population to the appropriate person-years at risk in the cohort.

**Results** The cohort yielded a total of 22,414 person-years. The SMR was 1.1 (95% CI: 0.9–1.5) with a value of 0.9 (95% CI: 0.6–1.5) among males and 1.2 (95% CI: 0.9–1.7) among females.

**Conclusion** The study provided further evidence that the main events in gastric carcinogenesis occur before adult life.

**Keywords** Gastric cancer, mortality, cohort study

**Accepted** 24 September 2001
differences in GC risk are mainly related to factors operating in the first two decades of life.2,3

In the present study, the mortality from GC observed in a cohort of husbands and wives of individuals who died from GC was compared with that of the general population. The rationale included the following assumptions: (1) people who died from GC were exposed to risk factors, (2) the strongest risk factors for these people were related to dietary habits and environmental conditions and exerted their main effects before the age of marriage, and (3) these people and their spouses shared the same living conditions during adult life. The purpose of the study was to demonstrate that, as expected, the spouses of patients who died from GC were not at increased risk of dying from the same disease compared to the general population.

Materials and Methods

Population

The study was conducted in the province of Forlì (Emilia-Romagna Region, north eastern Italy), covering a surface area of 2390 km² (72% hills and mountains, 28% plains). According to updated figures from the census offices of the borough councils, the population of the province currently stands at 351 000. In 1951, the proportion of the active population employed in agriculture was as high as 53%. A progressive decrease has been observed since then, leading to the current figure of 10%. In the area, GC is a major public health problem. Among males, the age-standardized (world standard population) mortality rate was 51.3 per 100 000 in 1969–1976, 48.0 in 1977–1984 and 35.6 in 1985–1988 (among females: 27.4, 22.9, and 17.2, respectively). Despite such a marked decrease,27 GC remains the second most frequent cause of death from cancer among males and the leading cause among females.28 Current age-standardized (world) incidence rates (39.3 per 100 000 males and 22.8 per 100 000 females)29 confirm that the province of Forlì is one of the areas at highest risk in the Western World.

Identification of gastric cancer deaths

The Italian National Statistics Bureau (ISTAT) provided us with copies of the tapes of official death records for residents of the province of Forlì for the period 1969 to 1988. As the computerized version of ISTAT death certificates is an anonymous abstract of the original one, the subjects who died from GC could be identified on the basis of the following items of information: name, date of birth; sex; marital status; month, year, and place of death. Each anonymous record was cross-checked with the mortality registry (registry of death certificates) made available by 27 of the 28 borough councils located in the area. Access to data was denied by the Public Records office of one small-sized community. As most of the 27 registries operating were not computerized in the years 1969–1988, the search for data was performed manually. If no person or two or more people in the mortality registry could be matched with one ISTAT record, the case was considered unidentified.

Identification of the cohort of spouses

Among GC deaths identified, the next step of the search was to select individuals who were married at the time of death. The death certificate provided essential information on this, i.e. marital status, name of wife or husband (if any) and date of marriage. To validate this information, each name was cross-checked with the entire mortality registry (to identify wives or husbands who had subsequently died) as well as the population registry (to identify those still alive). The date of marriage was used as further confirmation and wives or husbands identified were entered into the cohort. In the event that both husband and wife had died from GC between 1969 to 1988, the spouse of the individual who died first was included in the cohort.

Statistical analysis

Descriptive data analyses were performed with the SAS package. The mortality from GC in the cohort compared with the general population was based on the calculation of the standardized mortality ratio (SMR) (the ratio of observed to expected number of GC deaths in the cohort) and 95% CI assuming a Poisson distribution for the observed frequency. The expected number of deaths was calculated by applying the sex, age (<45, 45–54, 55–64, 65–74, >74 years), and time period (1969–1976, 1977–1984, 1985–1988) specific mortality rate in the general population to the appropriate person-years at risk in the cohort. The denominators for these rates were based on census data (years 1971, 1981, and 1991). The person-years at risk were computed for each individual in the cohort from the date of death of wife or husband until the date of death or the end of follow-up (31 December 1988) for those known to be alive. For this procedure we used the EPICURE package. A Poisson multiple regression model was built to assess the independent effect of age, sex, and time period on SMR. For this procedure the EGRET package was used.

Results

As shown in Table 1, a total of 4348 anonymous GC death records were provided by ISTAT. Among these, 4301 records (98.9%) were successfully matched with those of the 27 mortality registries, leading to patient identification. The rate of identification was 2531/2563 (98.6%) for males and 1770/1785 (99.2%) for females. Death certificates indicated that 2759 (64.1%) of the patients identified were married on the day of death. Among these, a further search led to the identification of 2720 (98.6%) wives or husbands.

Table 1 Identification of the study cohort

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients identified</td>
<td>2563</td>
<td>1785</td>
<td>4348</td>
</tr>
<tr>
<td>Patients unidentified</td>
<td>32</td>
<td>15</td>
<td>47</td>
</tr>
<tr>
<td>Widowed/unmarried</td>
<td>457</td>
<td>1085</td>
<td>1542</td>
</tr>
<tr>
<td>Married</td>
<td>2074</td>
<td>685</td>
<td>2759</td>
</tr>
<tr>
<td>Wife or husband unidentified</td>
<td>29</td>
<td>10</td>
<td>39</td>
</tr>
<tr>
<td>Wife or husband identified</td>
<td>2045</td>
<td>675</td>
<td>2720</td>
</tr>
</tbody>
</table>

a The anonymous death records provided by the Italian National Statistics Bureau were cross-checked with the mortality (death certificate) registries of 27/28 borough councils of the province of Forlì using the following items of information: month and year of birth; sex; marital status; and month, year, and place of death.

b Name of wife or husband (if any) and date of marriage as reported in the death certificate were cross-checked with the entire mortality registry (to identify those who had subsequently died) as well as the population registry (to identify those still alive). The wives or husbands identified entered into the cohort.
Table 2 shows the distribution by sex, age, and follow-up status on 31 December 1988 for the 2720 spouses in the cohort. Only 13 individuals were lost to follow-up. The observed number of GC deaths was 52.

The cohort yielded a total of 22,414 person-years. The expected number of GC deaths was estimated to be 46.5. With an observed number of 52 deaths, the SMR was 1.1 (95% CI: 0.9–1.5). The SMR was 0.9 (95% CI: 0.6–1.5) for males and 1.2 (95% CI: 0.9–1.7) for females.

Table 3 shows that sex, age at entry, and time period had no significant effect on the relative risk of dying from GC, given death of a spouse from the condition.

**Discussion**

We consider it necessary to comment on both the methodology and rationale of this study. Firstly, our aim was to support and not to refute the null hypothesis. Thus, the issue of the statistical power was a critical one. The study was restricted to the province of Forlì because access to information was easier and the reported GC mortality was greater than that of neighbouring areas in Romagna. The cohort yielded 22,414 person-years with 46.5 expected GC deaths. The observed number was 52 for an SMR of 1.1 (that is, a non-significant increase in the risk of fatal GC). Based on these findings, we estimated that the study had a 92% power to demonstrate a 50% increase in the risk of GC death or an SMR of 1.5 (corresponding to 70 observed deaths). Although unplanned, such a level of power appeared to be an acceptable one.

The second major issue concerning the study methods was the potential reduction in accuracy associated with the manual cross-check of each of the 4348 anonymous records provided by ISTAT with each of the 27 population registries available. Albeit reasonable, our pessimistic expectations were not confirmed. The paperwork archives of the borough councils were found to be in good order, which minimized the frequency of unmatched cases. Most of the 47 (or 1.1%) cases unidentified could be attributed to a small-sized rural community where access to information was denied by the census office. In other words, the identification method based on the items of information provided by ISTAT (month and year of birth; sex; marital status; and month, year, and place of death) was associated with a negligible proportion of potential multiple matchings. This was greatly facilitated by the small size of the borough councils and, thus, of their mortality registries.

The assumptions supporting the study rationale also need to be discussed. The essential assumption that people who died from GC were heavily exposed to risk factors was based on the obvious fact that they had a cumulative risk of GC death of 100%. We also assumed that the most important aetiological factors for these people were exogenous and exerted their main effects before the age of marriage. Both assumptions are in accordance with the current concepts in GC epidemiology. It is noteworthy that we could neither demonstrate nor exclude that these factors persisted after marriage. In theory, people who died from GC could also have adopted the ‘healthy’ lifestyle habits of their spouses. Anyway, we assumed that individuals who died from GC and their spouses shared the same lifestyle during adult life. Although smoking habits, alcohol consumption, drug consumption, and exposure to environmental agents may have differed between husbands and wives, many other standards of living, including potentially important determinants of GC risk such as the basic composition of the diet, were probably the same. This is supported by historical and socioeconomic considerations. Although information on the employment history of people who died from GC and their spouses was not available, it should be pointed out that, with the exception of the most recent generations, the population of Forlì has been characterized by poor income levels coupled with a predominance of agricultural work and other resident occupations. This suggests that all members of the families were likely to have their meals at home and that the type of meals seldom varied. In brief, we assumed that critical differences in dietary habits between participants who died from GC and their spouses would mainly have occurred before marriage.

Some limitations in study conduct and analysis need to be mentioned. Firstly, the study was not based on histologically confirmed cases. The study area was covered by cancer registration only at the end of the 1980s. However, a study carried...
out by the Department of Health in all the provinces of the Emilia-Romagna Region documented acceptable levels of completeness and accuracy of death certificates. Secondly, analysis was not stratified by age at wedding nor duration of marriage. Only 46% of original death certificates reported information regarding age at wedding (median, 23 years; ≥18 years for 97% of classifiable individuals) and, consequently, duration of marriage (median, 41 years; ≥20 years for 93% of classifiable subjects; data not shown). Thirdly, death certificates did not provide the place of birth. Marked geographical variation in GC incidence and mortality in Italy suggests that this was a factor of importance in the risk estimate. In fact, poor socioeconomic standards in the study area have limited immigration until recently.

The design of our study has some analogies with that of migrant studies, albeit with a reverse approach. Migrant studies have generally dealt with populations moving during adult life from high-risk countries to low-risk countries. Susceptibility to GC has been consistently found to be strongly related to the place of origin, and much less to the place of subsequent residence. In the present study, we considered a cohort of people who physically moved, at the time of marriage, to live with a population of individuals who had a cumulative risk of GC death of 100%. The results showed that adult life for these spouses did not convey an increased risk of dying from GC compared with the general population. Whatever lifestyle was adopted by these new families, critical differences in exposure to risk factors could have occurred only before the age of marriage. Albeit indirectly, this confirms that the main events in gastric carcinogenesis occur early in life.

Acknowledgements

The authors wish to thank B Bondi (Cesena Health Care District), PL Cesari, M Veronesi (Rimini Health Care District), M Fabi (Langhirano Health Care District), R Ricci (Forlì Health Care District), and C Zacchetti (Epidemiology Service, Lombardy Region, Milan, Italy) for their collaboration. This study was supported by research grants no. 3285/93 and 3096/95 from the Department of Health, Emilia-Romagna Region, Bologna, Italy.

KEY MESSAGES

- In a cohort of people who lived their adult life with people who died of gastric cancer (GC), the risk of dying from the disease was not significantly increased compared with that of the general population.
- Assuming that people who died from GC were heavily exposed to environmental risk factors for GC and that these people and their spouses shared the same life conditions only during adult life, it was suggested that critical differences in exposure to risk factors occurred before the age of marriage.
- Albeit indirectly, it was confirmed that the main events in gastric carcinogenesis occur early in life.

References

Commentary: Preventable causes of gastric cancer may also operate in adult life

David Coggon

"Jack Spratt would eat no fat, his wife would eat no lean
And so between the two of them they licked the platter clean."

The children’s rhyme about Jack Spratt and his wife will be familiar to British readers, but Nanni and colleagues believe that married couples such as the Spratts are an exception, at least in northern Italy. They assume that during adult life the exposures of husbands and wives to dietary and other risk factors for stomach cancer will generally be similar. Thus, they interpret their observation that spouses of stomach cancer cases experience mortality from the disease similar to that of the general population as evidence that the main events in gastric carcinogenesis occur before adult life. The implication is that the search for effective means of prevention should focus on the environment in childhood, or perhaps even earlier.

Certainly there is strong evidence from migrant studies that major risk factors for stomach cancer, or at least for the histological subset of intestinal-type tumours, operate at young ages. One such factor is likely to be infection by Helicobacter pylori. Several prospective cohort studies have indicated that *H. pylori* infection carries an increased risk of later gastric cancer. Furthermore, prevalent *H. pylori* infection in adults has been linked with domestic crowding in childhood, and in England and Wales, mortality from stomach cancer has been correlated geographically with crowding in homes some 40 years earlier.

However, it does not necessarily follow from Nanni’s findings that important preventable causes for stomach cancer do not act also during adult life. It may just be that, in the Italian population studied, these risk factors did not vary greatly from person to person, or at least no more than between husbands and their wives. Indeed, case-control studies have found quite consistently that higher consumption of fresh fruit and vegetables as an adult is associated with a lower risk of gastric malignancy.

Two other conceptual points from Nanni’s paper are worth highlighting. One is the reference to a long induction period being a feature of stomach cancer. Strictly, an induction period is not a characteristic of a disease, but of the relationship between a disease and one of its causes. Thus, the same disease may have one cause that acts with a long induction period, and another that alters risk within a short time from exposure.

The other contentious point is the assumption that people who have died from stomach cancer must have been heavily exposed to risk factors, since their cumulative risk of death from the disease was 100%. It is correct that they must have been exposed to a combination of causes sufficient to induce the disorder, but we should not assume that these causes are necessarily identifiable or measurable risk factors. They could, for example, be unobservable ‘chance’ events at a molecular level. An analogy can be drawn with the tossing of a coin. The fact that a coin has come down heads does not imply that it must have been heavily exposed to any risk factors for this outcome. Rather, the observation may reflect a combination of a complex set of circumstances (the dimensions, shape and weight of the coin; the exact forces acting on it and its height above ground when tossed; the viscosity of the air and wind speed; the contour and rigidity of the surface onto which it falls etc), none of which on its own could be shown to have a consistent impact on whether coins come down heads or tails.

As a corollary, the fact that the causes of a disease are only partially understood’ and that we do not know why some...
people get it and others do not (even when their exposure to established risk factors appears identical), does not necessarily imply that there must be other major causes waiting to be identified. Of course, it may still be worth looking for such causes in case they exist.

References