Background and aims: Two divergent patterns of mortality for smoking related diseases in ulcerative colitis and Crohn’s disease patients were suggested in a previous population based study in Florence, Italy. Long term follow up (median 15 years) was completed to re-evaluate mortality in this Mediterranean cohort.

Patients and methods: Overall, 920 patients with inflammatory bowel disease were followed until December 2001 or death, with seven patients (0.8%) lost to follow up. A total of 14 040 person years were available for analysis; 118 deaths were observed (81/689 in ulcerative colitis and 37/231 in Crohn’s disease). Expected deaths were estimated using age, sex, and calendar specific national and local mortality rates; standardised mortality ratios (SMR) and 95% confidence interval (CI) were calculated.

Results: Among Crohn’s disease patients, mortality was strongly increased for gastrointestinal diseases (SMR 4.49 (95% CI 1.80–9.25)), all cancers (SMR 2.10 (95% CI 1.22–3.36)), and lung cancer (SMR 4.00 (95% CI 1.60–8.24)), leading to a significant 50% excess total mortality. Ulcerative colitis patients showed a significantly reduced total mortality because of lower cardiovascular (SMR 0.67 (95% CI 0.45–0.95)) and lung cancer (SMR 0.32 (95% CI 0.07–0.95)) mortality. No significant excess for colorectal cancer mortality was evident in this extended follow up.

Conclusions: These clearly divergent patterns of mortality correlate with documented differences in smoking habits between Crohn’s disease and ulcerative colitis patients. Family doctors and gastroenterologists should consider stopping cigarette smoking a specific priority for Crohn’s disease patients; the latter should be offered free participation in structured programmes for smoking cessation, with the aim of reducing smoking related excess mortality. Overall, no evidence of an increased mortality for large bowel cancer emerged in this series.

METHODS
A previous population based epidemiological study identified all patients aged at least 15 years with a diagnosis of UC or CD residing in the metropolitan area of Florence during the period 1978–1992. Overall, 920 patients with a diagnosis of IBD were followed from enrolment until death or the end of the follow up period (31 December 2001). Four patients had left the country and were censored at the date of migration abroad; three of the 63 patients who migrated elsewhere in Italy could not be traced and were also censored. Overall, therefore, the vital status at the end of follow up was not available for seven (0.8%) patients, who were considered for analysis only until the date of migration.

We report here the results of a long term mortality follow up (median 15 years) carried out to re-evaluate the patterns of mortality in this population based cohort, the only one so far available in a Mediterranean country.

Abbreviations: CD, Crohn’s disease; IBD, inflammatory bowel disease; SMR, standardised mortality ratio; UC, ulcerative colitis
of the International Classification of Diseases (ICD IX). Expected deaths were estimated on the basis of five year age groups, sex, and calendar year specific national mortality rates. Standardised mortality ratios (SMRs) were estimated for overall mortality and selected groups of causes, including specific cancer sites; 95% confidence intervals (CI) were calculated based on the assumption of a Poisson distribution for deaths observed in the follow up period. Analyses were carried out separately for UC and CD and for each IBD type by sex. In the estimation of expected deaths due to cancer of the colon or rectum, the follow up period at risk was censored at the date of surgery in a subgroup of 52 patients (5.7%) who had undergone total colectomy and/or rectum resection during the study period, as appropriate.

The same analyses were also carried out using local mortality rates in order to take into account possible local specific patterns of mortality. Only results based on national rates (which are more stable being based on much larger numbers of deaths) are shown, except for two specific results concerning non-cancer causes of death, only mortality due to gastrointestinal disease was increased, although not significantly (SMR 1.57 (95% CI 0.78–2.81)) with two deaths from non-Hodgkin’s lymphoma. Two deaths due to cancer of the hepatobiliary system were observed versus 2.5 expected, with two deaths from non-Hodgkin’s lymphoma. Two deaths due to gastrointestinal mortality was evident (SMR 1.26 (95% CI 0.34–3.24)) based on four observed deaths.

Considering non-cancer causes of death, only mortality due to gastrointestinal disease was increased, although not significantly (SMR 1.57 (95% CI 0.78–2.81)), based on 11 observed deaths. Among these 11 deceased subjects, five died from causes directly related to UC (two surgical complications, one toxic megacolon, one sigma perforation, and one intestinal infarction) while in three cases the death certificate mentioned only UC and cardiovascular insufficiency as the condition eventually leading to death; two deaths were related to complications of duodenal and gastric ulcer, respectively, and one to pancreatitis. This increased risk was more evident and reached statistical significance in the analysis carried out using local mortality rates (SMR 2.12 (95% CI 1.05–3.80)). No other relevant differences were evident using local rates.

No remarkable differences in total and cause specific mortality emerged in the analyses carried out separately by sex.

### Crohn’s disease patients
The results obtained for the subcohort of CD patients are reported in table 2. For general mortality, a significant 50% increase was evident (SMR 1.51 (95% CI 1.06–2.08)) based on 37 observed deaths (16 in males and 21 in females) and 24.55 expected. Deaths due to non-malignant gastrointestinal causes were significantly increased (SMR 4.49 (95% CI 0.71–1.04)) based on the observation of 81 deaths (53 in males and 28 in females) (table 1). This result was mostly due to a significantly reduced number of cardiovascular deaths (SMR 0.67 (95% CI 0.45–0.95)) and to a reduction in total cancer mortality (SMR 0.71 (95% CI 0.47–1.04)). In the latter group of causes, lung cancer mortality was strongly and significantly reduced (SMR 0.32 (95% CI 0.07–0.95)). A non significant excess of deaths from haemolymphopoietic malignancies was observed (four cases versus 2.5 expected), with two deaths from non-Hodgkin’s lymphoma. Two deaths due to cancer of the hepatobiliary system were observed versus 1.90 deaths expected. No excess for colorectal cancer mortality was evident (SMR 1.26 (95% CI 0.34–3.24)) based on four observed deaths.

### UC patients
General mortality was significantly lower (30%) than expected in UC patients (SMR 0.70 (95% CI 0.56–0.88))

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>ICD IX</th>
<th>Observed (n)</th>
<th>Expected (n)</th>
<th>SMR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplasms</td>
<td>140–208</td>
<td>26</td>
<td>36.50</td>
<td>0.71</td>
<td>(0.47–1.04)</td>
</tr>
<tr>
<td>Digestive system</td>
<td>150–159</td>
<td>11</td>
<td>12.74</td>
<td>0.86</td>
<td>(0.43–1.55)</td>
</tr>
<tr>
<td>Stomach</td>
<td>151</td>
<td>2</td>
<td>3.31</td>
<td>0.60</td>
<td>(0.07–2.18)</td>
</tr>
<tr>
<td>Colon-rectum</td>
<td>153–154</td>
<td>4</td>
<td>3.16</td>
<td>1.26</td>
<td>(0.34–3.24)</td>
</tr>
<tr>
<td>Liver</td>
<td>155</td>
<td>2</td>
<td>1.90</td>
<td>1.05</td>
<td>(0.12–3.80)</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>160–165</td>
<td>3</td>
<td>10.43</td>
<td>0.29*</td>
<td>(0.06–0.84)</td>
</tr>
<tr>
<td>Lung</td>
<td>162</td>
<td>3</td>
<td>9.25</td>
<td>0.32*</td>
<td>(0.07–0.95)</td>
</tr>
<tr>
<td>Breast</td>
<td>174</td>
<td>2</td>
<td>1.98</td>
<td>1.01</td>
<td>(0.11–3.65)</td>
</tr>
<tr>
<td>Haematopoietic system</td>
<td>200–208</td>
<td>4</td>
<td>2.54</td>
<td>1.57</td>
<td>(0.42–4.03)</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>200–202</td>
<td>2</td>
<td>0.83</td>
<td>2.41</td>
<td>(0.27–8.70)</td>
</tr>
<tr>
<td>Other neoplasms†</td>
<td>6</td>
<td>8.81</td>
<td>0.68</td>
<td>(0.25–1.48)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>250</td>
<td>2</td>
<td>3.58</td>
<td>0.56</td>
<td>(0.06–2.02)</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>390–459</td>
<td>31</td>
<td>46.32</td>
<td>0.67*</td>
<td>(0.45–0.95)</td>
</tr>
<tr>
<td>Gastrointestinal diseases</td>
<td>520–579</td>
<td>11</td>
<td>7.01</td>
<td>1.57</td>
<td>(0.78–2.81)</td>
</tr>
<tr>
<td>Violent causes</td>
<td>800–998</td>
<td>5</td>
<td>6.09</td>
<td>0.82</td>
<td>(0.26–1.92)</td>
</tr>
<tr>
<td>Other causes‡</td>
<td>6</td>
<td>15.49</td>
<td>0.39*</td>
<td>(0.14–0.84)</td>
<td></td>
</tr>
<tr>
<td>All deaths</td>
<td>001–999</td>
<td>81</td>
<td>11.99</td>
<td>0.70*</td>
<td>(0.56–0.88)</td>
</tr>
</tbody>
</table>

SMR, standardised mortality ratio; 95% CI, 95% confidence interval.
†This category includes six deaths from cancer of the following sites: bone, endometrium, prostate, bladder, adrenal gland, and one unknown primary site.
‡This category includes six deaths from other causes (infectious disease, AIDS, pulmonary oedema, renal failure, arthritis, and one death abroad for which it was not possible to retrieve the death certificate).

*p<0.05.
Divergent patterns of total and cancer mortality

1.80–9.25) based on seven cases; two of these deaths were directly related to CD (one intestinal infarction and one intestinal bleeding) and in two cases the death certificate mentioned only CD and cardiovascular insufficiency as the condition eventually leading to death. Three deaths were due to non-alcoholic cirrhosis. Also, total cancer mortality was significantly increased (SMR 2.10 (95% CI 1.22–3.36)) (table 2), particularly lung cancer mortality (SMR 4.00 (95% CI 1.60–8.24)). Only one death from colorectal cancer was reported (0.71 expected). The increased mortality for gastrointestinal disease was even more evident in the analysis carried out using local mortality rates (SMR 6.14 (95% CI 2.46–12.65)). No other relevant differences were evident using local rates.

No remarkable differences in total and cause specific mortality emerged among CD patients according to gender.

Smoking habits of deceased IBD patients

Information on smoking habits was retrieved for 113 of 118 deceased patients (95.76%) from available clinical records or interviews of next of kin (table 3). Smoking history at diagnosis of IBD for deceased subjects was reported by 22 UC (28.57%) and only four CD patients (11.11%). All seven CD patients deceased from lung cancer were current (n = 5) or former (n = 2) smokers; on the other hand, among the three UC patients deceased from lung cancer, one was a never smoker at diagnosis and until death, one was a former smoker, and the other one was reported as a current smoker at diagnosis.

DISCUSSION

The results of this population based study clearly confirm the existence of two specific and divergent patterns of mortality among UC and CD patients that correlate with well known differences in smoking history between the two conditions. These differences have been documented among deceased subjects in our cohort, confirming a higher prevalence of current smokers among CD patients.

In UC patients, a significant reduction in total mortality was evident due to a cardiovascular mortality significantly lower than in the general population. Total cancer mortality was also reduced in these patients, with a 70% reduction in lung cancer mortality. In contrast, total mortality was 50% higher in CD patients in comparison with the general population. This excess was related to a fivefold increase in mortality due to gastrointestinal diseases and to an increase in total cancer mortality, mostly due to a fourfold increase in lung cancer mortality.

We have previously shown that IBD incidence rates increased in this population over a 15 year period in the Florence metropolitan area; a capture-recapture analysis showed that our case ascertainment was accurate in comparison with other studies. Follow up of this large series was almost complete and no selected loss occurred. The analyses were carried out using both national and local mortality rates in order to take into account possible geographical differences in rates, but the results were very similar.

Most reports have described a low or only slightly increased mortality for UC patients. In a recent study in a Danish population based cohort of 1160 UC patients with a median follow up of 19 years, total mortality was similar to the general population. A few Northern European studies, on the other hand, have reported moderately increased mortality. A significant excess mortality in CD patients has been reported in population based mortality studies.

A specific pattern of smoking habits, traditionally reported as negatively associated with UC, probably contributed to the reduced mortality for a group of smoking related causes,
including lung cancer and cardiovascular deaths, in UC patients. A reduction in mortality for cancer of the respiratory system has also been reported in a multicentre hospital based study in a large series of Italian UC patients.6 Increased mortality for respiratory diseases in UC has been reported by others6 7 8 9 but was associated with asthma or pneumonia more than bronchitis and emphysema. Five cancer incidence studies carried out in the UK, Denmark, Sweden, Canada,22–25 and in our Florence IBD cohort30 reported a decrease in lung cancer incidence in UC patients.

In contrast, long term treatments based on salicylates may also have contributed to reduced cardiovascular mortality.12 The smoking history of CD patients has been consistently reported as being characterised by a much higher frequency of current smokers in comparison with the general population.21 22 23 24 A 40% excess mortality for lung cancer, approaching the level of statistical significance, was reported in a study on hospitalised CD patients in Denmark27 while two cancer incidence studies showed an increased risk for lung cancer.25 26 It is noteworthy that CD patients in our study showed a fourfold excess of mortality for gastrointestinal diseases, mostly related to specific complications. Smoking has been reported to be an independent risk factor for recurrence of CD, influencing disease activity after surgery27 and clinical relapse.10 11 Benefits of smoking cessation on the clinical course of the disease and therapeutic needs have also been suggested by an intervention study.12 Overall no evidence of an increased mortality for large bowel cancer emerged in this series. In our analysis, we also took into account the proportion of patients who had undergone extensive colorectal surgery, censoring their observation time at that exact date, thus reducing the number of expected cases of colon and/or rectal cancer in the site specific analyses. Long term maintenance treatment has been advocated by most clinicians in the Florence area.33 A reduced risk for colorectal cancer in UC patients actively treated with anti-inflammatory drugs has been reported15 and also experimental data suggest that mesalazine has anti-inflammatory properties and can affect the proliferation of colon epithelial cells.16 Overall, however, population based studies in the last decade have reported estimates of colorectal cancer mortality substantially lower17–19 in comparison with earlier studies, and some studies reported no significant differences in colorectal cancer mortality among UC patients in comparison with the general population.20 An increased risk for colorectal cancer has been consistently reported in most population based cancer incidence studies in UC patients,20–23 25 27 with a few exceptions.24 A strong increase in the incidence of colorectal cancer has been reported in clinical series of UC patients followed by referral centres23 24; similar studies have also reported increased risks for both CD and UC patients with extensive colitis.15 In contrast, CD patients did not show an increased risk of colorectal cancer in population based incidence studies,18 26 27 29 31 with few exceptions.25 26 In conclusion, the long term follow up results of this relatively large population based series of IBD patients identified in a Mediterranean country have shown two clearly divergent mortality patterns for UC and CD, particularly evident for lung cancer, with a 70% reduction and a fourfold increase in risk, respectively.

Smoking habits appear to contribute significantly to the increased mortality observed in CD. Considering the other negative effects on the clinical course of the disease, family doctors and gastroenterologists following CD patients should consider cessation of cigarette smoking a specific priority for these patients, often young and with a long life expectancy. Free participation in structured programmes for smoking cessation should be offered, with the aim of reducing smoking related excess mortality.

ACKNOWLEDGEMENTS

The authors acknowledge the support of other members of the Florence IBD Study Group (particularly Franco Pacini, Monica Milla, and Gabriella Nesia), the cooperation of the local association of IBD patients (AMIGL), the Regional Mortality Registry (RMR-CSPO, Florence), and Vanessa Visentin for editorial assistance. The study was supported by Regione Toscana, Florence, Italy.

Authors’ affiliations

G Masala, M Ceroti, C Saieva, I Zanna, D Palli, Molecular and Nutritional Epidemiology Unit, CSPO-Scientific Institute of Tuscany, Florence, Italy
S Bagnoli, G Trollori, Department of Gastroenterology, AO Careggi, Florence, Italy
G d’Albasio, Department of Gastroenterology, AO Careggi, Florence, Italy, and Regional IBD Referral Centre, Florence, Italy

REFERENCES


G Masala, S Bagnoli, M Ceroti, C Saieva, G Trallori, I Zanna, G d'Albasio and D Palli

Gut 2004 53: 1309-1313
doi: 10.1136/gut.2003.031476

Updated information and services can be found at:
http://gut.bmj.com/content/53/9/1309

These include:

References
This article cites 39 articles, 6 of which you can access for free at:
http://gut.bmj.com/content/53/9/1309#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

- Ulcerative colitis (1113)
- Colon cancer (1547)
- Drugs: gastrointestinal system (207)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/