Mortality in patients with coeliac disease and their relatives: a cohort study

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Summary

Background Although previous studies have shown increased mortality in patients with coeliac disease and their relatives, no data are available in relation to different patterns of clinical presentation. We assessed mortality in patients with coeliac disease and their first-degree relatives.

Methods We enrolled, in a prospective cohort study, 1072 adult patients with coeliac disease consecutively diagnosed in 11 gastroenterology units between 1962 and 1994, and their 3384 first-degree relatives. We compared the number of deaths up to 1998 with expected deaths and expressed the comparison as standardised mortality ratio (SMR) and relative survival ratio.

Findings 53 coeliac patients died compared with 25·9 expected deaths (SMR 2·0 [95% CI 1·5–2·7]). A significant excess of mortality was evident during the first 3 years after diagnosis of coeliac disease and in patients who presented with malabsorption symptoms (2·5 [1·8–3·4]), but not in those diagnosed because of minor symptoms (1·1 [0·5–2·2]) or because of antibody screening (1·2 [0·1–7·0]). SMR increased with increasing delay in diagnosis and for patients with poor compliance with gluten-free diet. Non-Hodgkin lymphoma was the main cause of death. No excess of deaths was recorded in relatives with coeliac disease.

Interpretation. Prompt and strict dietary treatment decreases mortality in coeliac patients. Prospective studies are needed to clarify the progression of mild or symptomless coeliac disease and its relation to intestinal lymphoma.

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Introduction

Findings from population-based studies have shown that the true frequency of coeliac disease is high[1] even in countries where it was thought to be rare.[2] An increased overall and cancer mortality has been reported in adult patients with coeliac disease[3,4] and their relatives,[5] which lends support to the clinical importance of this disorder. Improved knowledge of the wide clinical spectrum of coeliac disease[6,7] and the use of powerful screening tests[8,9] have radically changed the pattern of presentation of this disorder. Previous mortality could be underestimated by the inclusion of subclinical and symptom-free patients, but no information is available on the prognosis of the new forms of coeliac disease. Additionally, the reported 1·9-fold[3] and 3·4-fold[4] increases in mortality might be excessive because some patients with a less favourable outcome, such as those with refractory sprue and intestinal lymphoma, were probably enrolled in those series.[10] The finding that the mortality excess is mainly accounted for by deaths occurring within a short time after diagnosis[3] indirectly lends support to this possibility.

We did a prospective study to find out whether differences in patterns of clinical presentation of coeliac disease are associated with differences in prognosis; whether age at diagnosis, time between onset of symptoms that subsequently led to intestinal biopsy (diagnostic delay), and degree of adherance with a gluten-free diet affect mortality; and whether first-degree relatives of these patients have an increased risk of mortality.

Methods

Patients

We identified patients with biopsy-proven coeliac disease from the records of the 11 gastroenterology units. The diagnostic criteria were subtotal or severe partial villous atrophy and crypt hyperplasia, and histological improvement after gluten-free diet. We enrolled 1072 consecutive patients older than 18 years at the time of diagnosis, between Jan 1, 1962, and 31 Dec, 1994, at 11 gastroenterology units. These units, evenly distributed through Italy, were selected from those participating in the Italian Club del Tenue study in accordance with the following inclusion criteria: completeness of clinical records (all the diagnoses of coeliac disease reported from the start of specific diagnostic activity), and reliability of the diagnoses throughout the entire period of activity. Units flagged patients by comparing records with the corresponding small-bowel pathology lists.

We obtained information on vital status, sex, age at time of diagnosis, date of initial presentation, diagnostic delay (time from onset of symptoms to intestinal biopsy), and dietary adherence (adherent or not adherent) recorded at presentation or during subsequent clinical surveillance. We classified patients into three subtypes of coeliac disease according to clinical presentation:[11] severe, with symptoms of malabsorption such as diarrhoea, weight loss, or both that led the patient to seek medical care; mild, with only trivial, transient, or seemingly

unrelated symptoms; and symptomless, which included symptom-free patients diagnosed during antibody screening.

Data collection

We interviewed the patients in the first few months of 1999 by telephone and asked about adherence to their gluten-free diet from the date of coeliac disease diagnosis. We classified diet as: gluten-free (no gluten intake); low gluten (occasional lapses, ie, 2–3 lapses per month); or containing gluten (frequent lapses, ie, once or more per week or no gluten restriction at all).[12] Further questions were about the date of birth, coeliac disease diagnosis, vital status, or date of death of first-degree relatives. For patients who had died, we obtained information from relatives or people who used to live with them. Date and place of death of these cases were also recorded. Researchers from eight of the 11 units agreed to interview 873 patients. Eight patients, or their relatives, could not be traced and three did not respond to the interview. Therefore 862 (80%) of 1072 patients were included in the second part of our study.

Cohort follow-up

We separated patients and their relatives into three cohorts. The first included all the 1072 patients with coeliac disease (patient cohort), for whom follow-up started at the time of diagnosis. The second included the parents of 862 patients (parent cohort), for whom follow-up started at the birth of the son or daughter with coeliac disease. The third group included all the siblings of 862 patients (sibling cohort), for whom follow-up started at birth. When two or more relatives were diagnosed in the same gastroenterology unit, we included the patient diagnosed first in the patient cohort, and the other patient or patients in the parent or sibling cohort. The end of follow-up was fixed at Dec 31, 1998, for all cohorts.

We ascertained the vital status of patients in all cohorts from the last known municipality of residence when this information could not be obtained from clinical records or interview. Copies of the death certificate for all patients who had died were obtained from the local mortality registry, and the cause of death was classified and coded according to the ninth revision of the International Classification of Diseases. For two unavailable death certificates, we obtained the causes of death from the death file from the Italian National Institute of Statistics.

Data analysis

We calculated the expected number of deaths in every unit by multiplying the number of patient-years in each stratum of sex, 5-year age-groups, and calendar year by the corresponding mortality rates. These rates were reported for each region covered by the units starting from 1960 to 1964 (patient cohort) or for the entire Italian population starting from 1900 to 1904 (parent and sibling cohorts). We calculated the standardised mortality ratios (SMRs [ratio of observed to expected deaths]), taking into account all-cause mortality and selected causes of death for the patient cohort, and all causes of death for the parent and sibling cohorts. The corresponding 95% CIs were calculated on the assumption that the observed number of deaths had a Poisson distribution. We stratified SMRs according to a series of demographic and clinical classifications and assessed differences by testing their heterogeneity between sex, pattern of presentation, and adherence with gluten-free diet, or for trend over strata (calendar year of initial presentation, age at diagnosis, and diagnostic delay) according to Breslow and Day's analysis.[13] Power calculations had suggested that the study would give an 80% chance of detecting significant overall SMRs higher than 1·6 (patient cohort), 1·2 (parent cohort), and 1·3 (sibling cohort), and a 2·3-fold higher SMR in patients with severe coeliac disease than in those with mild disease.[13]

We compared observed and expected cumulative overall survival proportions within each cohort. Expected proportions were calculated according to the national sex, age, and calendar-year life tables.[14] We presented results as relative survival ratios, and the corresponding 95% CI were based on the normal approximation of the binomial distribution. We used several statistical tests (χ^2 and its version for the trend, parametric or non-parametric one-way analysis of variance) when appropriate to test differences or trends in distribution of a factor between the classifications of another factor and among gastroenterology units. For all hypotheses tested, two-tailed p values less than 0·05 were deemed significant.

Results

Two of the 11 gastroenterology units flagged patients from before 1974, four flagged from 1975 to 1984, and the remaining five flagged after 1985. Median number of patients per unit was 48 (IQR 29–144). Complete data were available except for diagnostic delay and dietary adherence from 68 and 89 clinical records, respectively. Distributions of patients' sex, age at diagnosis, diagnostic delay, pattern of presentation, and adherence with gluten-free diet did not significantly differ between units. In the first cohort that included all 1072 coeliac disease patients, the ratio of men to women was 1/3; mean age at diagnosis 35·7 years (SD 14·1); mean follow-up 6·0 years (SD 4·9); and median diagnostic delay 17 months (IQR 4–122).

Table 1 shows mortality for the patient cohort by demographic classifications. 50 patients were lost during follow-up. An increase in mortality was noted in the entire patient cohort. The overall SMR did not differ by sex, age at diagnosis, or year of presentation. By contrast, SMRs increased significantly for patients with diagnostic delay more than 1 year, and we noted a significant association between increasing SMR and diagnostic delay. Nearly 50% of patients were diagnosed with mild or symptomless coeliac disease. There was a significant excess of deaths among patients who presented with only malabsorption symptoms. No excess mortality was seen in patients with mild or symptomless coeliac disease, and SMRs were heterogeneous between classifications of clinical patterns.

Significant excess of mortality was seen in patients who did not adhere to a gluten-free diet, recorded from clinical records (SMR 10·7 [95% CI 6·0–17·1]) and interview (6·1 [4·2–8·6]). However, the methods of assessing adherence to a gluten-free diet showed an important disparity. 95 (10%) of 915 patients who reported good adherence in clinical records admitted frequent dietary lapses at the direct interview. However, 16 (24%) of 68 patients who were classified as non-adherent in clinical records turned out to be strictly adherent at interview. For 627 patients, interview and clinical records showed probable adherence. For 155, the two methods showed agreement for probable non-adherence. The status of adherence was unknown for 290 patients because they were not searched for, traced, or did not attend interview, and were classified as uncertain. After this new classification, SMRs differed between classifications, and significant excesses of mortality were noted in probable non-adherent patients and in patients classified as uncertain.

	Patients	Patient-years	Observed deaths	Expected deaths	SMR (95% CI)	p
Overall	1072 (100%)	6444	53	25·9	2·0 (1·5–2·7)	<0·0001
Sex						
Men	258 (24%)	1446	22	11·0	2·0 (1·3–3·0)	0·004
Women	814 (76%)	4998	31	14·9	2·1 (1·4–3·0)	0·0003
				Test for heterogeneity: p=0·99		
Age at diagnosis (years)						
18–29	373 (35%)	2080	3	1·2	2·5 (0·5–7·3)	0·24
30–49	507 (47%)	3293	14	5·9	2·4 (1·3–4·0)	0·006
⩾50	192 (18%)	1071	36	18·8	1·9 (1·3–2·6)	0·0005
				Test for trend: p=0·46		
Year of presentation						
1962–74	29 (3%)	563	8	2·5	3·2 (1·4–6·3)	0·008
1975–84	156 (15%)	2002	14	7·6	1·8 (1·0–3·1)	0·05
⩾1985	887 (83%)	3879	31	15·8	2·0 (1·3–2·8)	0·0009
				Test for trend: p=0·38		
Diagnostic delay (months)						
⩽12	344 (32%)	2081	19	12·7	1·5 (0·9–2·3)	0·12
12–119	320 (30%)	2030	19	7·3	2·6 (1·6–4·1)	0·0004
⩾120	273 (25%)	1706	15	3·9	3·8 (2·2–6·4)	<0·0001
Unknown or not applicable*	135 (13%)	627	0	2·0		
				Test for trend: p=0·004		
Pattern of presentation						
Severe	590 (55%)	4255	43	17·2	2·5 (1·8–3·4)	<0·0001
Mild	415 (39%)	1870	9	7·9	1·1 (0·5–2·2)	0·79
Symptomless	67 (6%)	319	1	0·8	1·2 (0·1–7·0)	0·99
				Test for heterogeneity: p=0·033		
Adherence to gluten-free diet						
Likely	627 (59%)	3794	5	10·5	0·5 (0·2–1·1)	0·16
Not likely	155 (15%)	998	26	4·3	6·0 (4·0–8·8)	<0·0001
Uncertain	290 (27%)	1652	22	11·1	2·0 (1·2–3·0)	0·005
				Test for heterogeneity: p<0·0001		

SMR=standardised mortality ratio. *Unknown in 68 patients (clinical records lacking this information) and not applicable in 67 patients with symptomless disease. Test for trend does not include this category.

Table 1: **Demographics, clinical features, and overall mortality of patient cohort**

SMR was increased for patients with a diagnostic delay of 120 months or more (2·5 [1·3–4·6), severe coeliac disease (2·9 [1·8–4·3), and poor adherence to a gluten-free diet (5·2 [3·4–7·8]) in the 887 patients who were diagnosed as having coeliac disease after 1985. In the same way, SMR was increased for patients with a diagnostic delay of 120 months or more (3·3 [1·5–6–2]) and poor adherence to gluten-free diet (5·5 [2·5–10·5) in the 590 patients with severe coeliac disease. This analysis was not done for patients with mild coeliac disease, because only nine deaths occurred in this group.

The number of patients decreased progressively from the earliest to the latest period for diagnostic delay of 120 months or more (15 [52%], 39 [25%], and 219 [25%]; p=0·028), malabsorption symptoms (26 [90%], 126 [80%], and 438 [49%]; p=0·0007), and for likely non-adherence (11 [38%], 40 [26%], and 104 [12%]; p=0·0005).

The number of patients who presented with a diagnostic delay of 120 months or more did not differ significantly between clinical pattern (153 [26%] and 20 [25%] in patients with severe and mild coeliac disease, respectively; p=0·70), and adherence classification (163 [26%] likely, 42 [27%] non-adherent, and 68 [23%] uncertain; p=0·63). Finally, the number of patients who were probable non-adherents did not vary significantly between clinical pattern (97 [16%] and 98 [12%] in those with severe and mild disease, respectively; p=0·91).

Table 2 shows the causes of death recorded in the patient cohort. There was a significant excess of deaths from malignant disease and from diseases of the respiratory and digestive tracts. Of the patients who died as a result of malignant disease, non-Hodgkin lymphoma was mentioned in two-thirds of death certificates; the other eight deaths from malignant disease did not exceed the number expected. The sites of these cancers were the stomach in two patients, small intestine in one, liver in two, pancreas in one, pleura in one, and unspecified leukaemia in one. Of the deaths from respiratory diseases, viral or bacterial pneumonia was mentioned on three death certificates, lung emphysema on one, and fibrosing alveolitis on one. Of the deaths due to diseases of the digestive system, ulcerative jejunoileitis and coeliac disease were mentioned on five and three certificates, respectively. Other deaths due to digestive diseases were not significantly in excess (SMR 1·7 [95% CI 0·6–3·7]).

Figure 1 shows the trend in relative survival ratios of the entire cohort of coeliac disease patients. Reductions were noted within the first 3 years after diagnosis (relative

Causes of death (ICD9 codes)	Observed deaths	Expected deaths	SMR (95% CI)	p
Malignant diseases (140–208)	24	9·1	2·6 (1·7–3·9)	<0·0001
Non-Hodgkin lymphoma (200 or 202)	16	0·2	69·3 (40·7–112·6)	<0·0001
Other malignancies	8	8·9	0·9 (0·4–1·8)	0·94
Circulatory system diseases (390–459)	7	9·9	0·7 (0·3–1·5)	0·46
Respiratory system diseases (460–519)	5	1·4	3·6 (1·1–8·4)	0·03
Digestive system diseases (520–579)	11	1·8	6·1 (3·0–10·9)	<0·0001
Other causes of death	6	3·7	1·6 (0·6–3·5)	0·34

Table 2: **Causes of death in patient cohort**

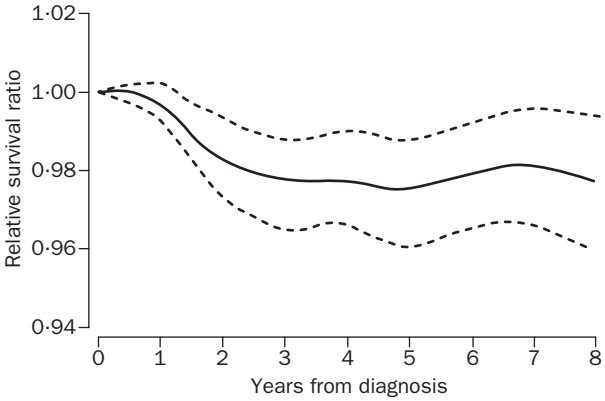

Figure 1: **Relative survival ratios and corresponding 95% CI for 1072 patients with coeliac disease**
Continuous line=relative survival ratio. Broken line=95% CI.

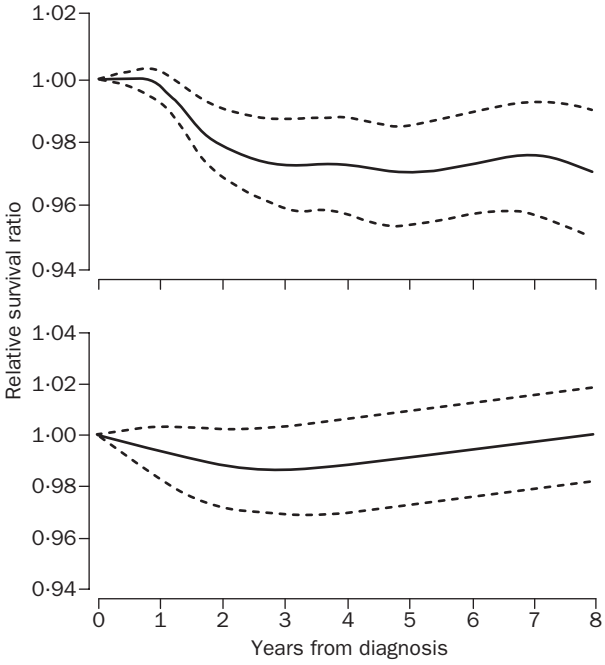

Figure 2: **Relative survival ratios and corresponding 95% CI for patients with severe (upper) and mild (lower) coeliac disease**
Continuous line=relative survival ratio. Broken line=95% CI.

survival ratio 0·98 [95% CI 0·97–0·98]). After this time, the ratio between observed and expected long-term survival probabilities stabilised (0·98 [0·96–0·99]). This finding is consistent with a 2% higher cumulative mortality in patients with coeliac disease than in the Italian population, and implies that the excess of mortality in these patients does not occur 3 years after diagnosis. Figure 2 shows the comparison between trends in relative survival ratios in patients classified according to the pattern of clinical presentation. Significant reductions in relative survival ratios were seen only for patients with severe symptoms at diagnosis, with a trend similar to that described for the entire cohort (0·97 [0·96–0·99] at 3 years from diagnosis; 0·97 [0·95–0·99] at 8 years). By contrast, observed and expected survivals did not differ significantly in the patients with mild coeliac disease. This analysis was not done for symptom-free patients, since only one death occurred in this group.

Table 3 shows the mortality of first-degree relatives of coeliac disease patients. Of 3384 relatives, 749 died during the follow-up period, and 741·6 deaths were expected. SMR did not differ significantly between relatives. 123 (4%) relatives were diagnosed with coeliac disease during their life. However, for these relatives, no significant difference between observed and expected deaths was noted.

Discussion

Our study on the mortality of coeliac disease was large with respect to the number of patients enrolled. Although the total number of patient-years at risk accumulated by our cohort (6444) was lower than that noted by Logan and colleagues[3] (8823), this difference is unlikely to have affected the accuracy of our mortality estimates, because previous studies[3,15] and our study agree that excess in mortality risk occurs mainly within the first years from diagnosis. Additionally, we have noted a relation between mortality and the pattern of clinical presentation, delay in diagnosis, and the degree of compliance with a gluten-free diet.

1072 adult patients with coeliac disease were consecutively diagnosed by 11 Italian gastroenterology units, in which researchers had similar diagnostic criteria for coeliac disease. This similarity was confirmed by the absence of significant differences for the variables shown in table 1. Because this study is not population-based, our design might have generated a selection bias. However, this possibility seems unlikely because the observed distribution of the clinical pattern of coeliac disease at presentation and of demographic factors did not differ from those reported by a large Italian multicentre survey.[16] Furthermore, compared with the unique population-based investigation,[3]

	Number	Person-years	Observed deaths	Expected deaths	SMR (95% CI)	p
Fathers						
All	862	26 673	337	340·7	1·0 (0·9–1·1)	0·87
With ascertained coeliac disease	22	659	7	8·4	0·8 (0·3–1·7)	0·80
Mothers						
All	862	29 538	259	243·3	1·1 (0·9–1·2)	0·33
With ascertained coeliac disease	15	466	4	3·7	1·1 (0·3–2·7)	0·82
Brothers						
All	822	27 655	80	72·3	1·1 (0·9–1·4)	0·39
With ascertained coeliac disease	27	1061	3	2·7	1·1 (0·2–3·3)	0·79
Sisters						
All	838	35 153	73	85·3	0·9 (0·7–1·1)	0·20
With ascertained coeliac disease	59	2327	5	5·7	0·9 (0·3–2·1)	0·82

SMR=standardised mortality ratio.

Table 3: **Mortality in 3324 first-degree relatives of 862 patients with coeliac disease**

we reported a lower mortality rate (8·2 *vs* 13·0 per 1000 patients per year) but an almost identical SMR (2·0 *vs* 1·9).

We therefore confirm a two-fold increase in overall mortality of adult patients with coeliac disease[3] and that this increase accounts for deaths within a short time from diagnosis.[3,15] These findings were not due to inclusion of patients who had disorders other than coeliac disease, because regrowth of villi after gluten-free diet was initially documented in all patients except for those who admitted a poor compliance with treatment from the beginning of the study. Our results were consistent with the fact that the duration of coeliac disease is often short before the onset or diagnosis of lymphoma.[17] Because most patients who died within 3 years of coeliac disease diagnosis had non-Hodgkin lymphoma, ulcerative jejunitis (regarded as a malignant disease strictly related to lymphoma)[18] or other tumours, the recorded excess of mortality during this time could be due to the occurrence of malignant disease, rather than to coeliac disease alone. After this time, the patients with coeliac disease who survived showed a probability of death similar to that of the general Italian population.

Although the severity of clinical presentation should relate to morbidity rather than to mortality of coeliac disease, most of the increased mortality (43 of 53 deaths) occurred in patients who presented with classic symptoms of malabsorption at diagnosis. By contrast, patients diagnosed with mild symptoms or by antibody screening did not show any relevant excess of mortality. These results are lent support by findings from two recent studies showing that patients with dermatitis herpetiformis (a disorder characterised by bullous skin disease, gluten-sensitive villous atrophy, and minor or absent malabsorption symptoms) have no increased general mortality.[19,20] Since symptom-free patients with coeliac disease are undetected and untreated for a long period of time, they might have an increased likelihood of developing lymphomas.[21] This possibility does not necessarily contradict our results. Patients who were originally subclinical or symptom free might have subsequently developed malabsorption symptoms (therefore classified as having a severe form of coeliac disease) because they already had a lymphoma (or other malignant disease) at the time of diagnosis, even though they transiently maintained their capacity to respond to gluten-free diet.[22]

We noted a positive association between diagnostic delay and SMR that rises to 3·8 in patients diagnosed 10 years or more after the onset of symptoms. Our results emphasise the need for prompt diagnosis and treatment also in those patients with a minor or symptomless form of coeliac disease. Nielsen and colleagues[4] did not show any difference in mortality risk for adult coeliac disease patients according to their adherance to gluten-free diet. However, Logan and colleagues,[3] noted a non-increased mortality rate in adult patients who had been on a strict gluten-free diet since diagnosis at childhood. Collin and colleagues,[23] reported a normal survival in a cohort of adult patients, 83% of whom adhered strictly to a gluten-free diet. Our results lend support to these studies because we paid greater attention to the reliability of the information on diet adherence.

We suspect that clinicians arbitrarily report poor adherence for patients who drop out because of death, whereas they probably report good adherence for those under closer medical surveillance. This suggestion could explain the high SMR (10·7) in patients classified as non-adherent on the basis of clinical records. However, the reliability of the information obtained directly from the patients is questionable[24] and the same might apply to interviews of relatives or collaterals of patients not traceable or who died during follow-up. Because of this unreliability, we expressed the degree of adherence to gluten-free diet by comparing the available information sources. All other dietary states were judged as uncertain or unknown.

By contrast with a previous study,[5] relatives of patients with coeliac disease did not show any excess of mortality compared with the general Italian population. Assuming that 338 (10%) of the 3384 relatives were affected by coeliac disease[25] and that this proportion of relatives had a two-fold increase in mortality, we should have seen 812 deaths. Of the 338 assumed coeliac patients, coeliac disease was diagnosed in only 123. Surprisingly, the SMR for these relatives was close to 1. However, mortality occurrence in relatives referred to the period after the birth of the index case (parents) or to their entire life (brothers and sisters). Thus, putative excesses of mortality occurring within a short time after diagnosis, were not appreciable for such a long follow-up period.

Our results confirm that the overall mortality in adult coeliac disease patients is double that of the general population, and show that delay in diagnosis, poor adherence to treatment, and severity of symptoms at presentation unfavourably affect patients' outlook. Prospective studies are needed to elucidate the progression of mild or symptomless coeliac disease and their relation to intestinal lymphoma. However, the normal survival of patients with these forms of disease should not discourage either an active search for these patients or their strict and life-long avoidance of dietary gluten.

The patients who died within a short time of diagnosis might have originally had a subclinical or symptomless form of the disease. Coeliac disease might have been subsequently unmasked by the onset and growth of malignant disease, and therefore the patient could have benefited from the protective effect of a gluten-free diet at an earlier stage.[26] Gluten-free diet, as well as decreasing mortality risk, has recently been shown to improve the quality of life even in patients with symptomless coeliac disease.[27]

Contributors

G Corrao and G R Corazza co-ordinated the study, designed the protocol, supervised the data at the co-ordinating centre, and wrote and edited the paper. V Bagnardi dealt with the mortality follow-up and collaborated with G Corrao in the statistical analyses. G Brusco, C Ciacci, M Cottone, C Sategna Guidetti, P Usai, P Cesari, M A Pelli, S Loperfido, U Volta, A Calabró, and M Certo obtained the data at individual study sites.

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