Malignancy in relatives of patients with coeliac disease

P. L. STOKES, PATRICIA PRIOR, T. M. SORAHAN, R. J. McWALTER*
J. A. H. WATERHOUSE, AND W. T. COOKE

The Nutritional and Intestinal Unit, The General Hospital, Birmingham, and the Department of Social Medicine, University of Birmingham, Birmingham B15 2TJ

Stokes, P. L., Prior, P., Sorahan, T. M., McWalter, R. J., Waterhouse, J. A. H., and Cooke, W. T. (1976). *British Journal of Preventive and Social Medicine*, 30, 17-21. **Malignancy in relatives of patients with coeliac disease.** A survey of 1329 relatives of 139 patients with coeliac disease demonstrated an overall increase of cancer deaths particularly in women, but this did not quite reach 5% significance in men. Evidence is insufficient to determine whether this was due to the occurrence of cancer in relatives with undetected coeliac disease or to the operation of independent factors.

The reports of malignancy in coeliac disease (Gough, Read, and Naish, 1962; Austad *et al.*, 1967; Harris *et al.*, 1967) leave little doubt that there is an increased incidence of such complication in this disorder. Malignant lymphoma of the jejunum has been the most common complication but gastrointestinal cancer, at sites other than the small intestine, has been shown to be almost as common.

Coeliac disease is also a familial condition with approximately 10% of first-degree relatives affected (Macdonald, Dobbins, and Rubin, 1965; Stokes, Asquith, and Cooke, 1973a). The mode of inheritance remains to be established but studies of histocompatibility (HL-A) antigens suggest that these, for example HL-A8, are important factors in the inheritance of the disease (Falchuk, Rogentine, and Strober, 1972; Stokes *et al.*, 1972). In animals certain HL-A antigens confer a predisposition to malignancy (Lilly, Boyse, and Old, 1964) although whether this is so in man is not clear. It is therefore possible that the relatives of coeliac patients who also have an increased incidence of HL-A8 antigen (Stokes *et al.*, 1973b) also have an increased incidence of malignancy. To explore this possibility, the incidence of malignancy in such relatives has been compared with that occurring in the population as a whole.

PROPOSITI, RELATIVES AND METHODS

The propoiti were 139 patients, 54 men and 85 women, each with the characteristic flat jejunal mucosa of coeliac disease who were under continued surveillance by the Nutritional and Intestinal Unit. The propoiti were selected on the basis of availability and co-operation. They were essentially those attending consecutive clinics and represented approximately one-half of the total clinic. In the 13 families in whom there was more than one coeliac, the patient first diagnosed was the propoitus. Two propoiti with malignant disease (lymphoma) died during this study.

The age distribution of the 139 propoiti at the time of diagnosis of coeliac disease is shown in Table I; there was no difference between the sexes. These individuals, in consultation with their immediate family and relatives, completed a questionnaire detailing the age of living relatives and age, date, and cause of death of those who had died. The questionnaires were discussed, clarified, and checked with the propoiti at their next attendance at the clinic. Malignancy as a cause of death was acceptable only if there was an unequivocal statement to that effect by the propoiti or other relative combined with supporting evidence such as the nature of an operation or other form of cancer treatment. Where there was cause for

*Deceased

TABLE I
AGE DISTRIBUTION OF PROPOSITI

Age at diagnosis (years)	Cases (No.)	Percentage
0-14	21	15.1
15-24	29	20.9
25-34	32	23.0
35-44	18	12.9
45-54	25	18.0
55-64	11	7.9
65-74	3	2.2
Total	139	100.0

doubt, the death certificate, case records of the hospital concerned with the clinical management or the files of the Birmingham Regional Cancer Registry were checked. If the cause of death (cancer or not), age at death, and year of death were not definitely known, that relative was excluded.

The distribution of 1329 relatives (654 men and 675 women) included in the survey are shown in Table II. There were 272 grandparents, 266 parents, 411 siblings of parents, and 380 siblings of propositi. The number and nature of cancer deaths

TABLE II
RELATIVES OF ADULT COELIAC DISEASE PROPOSITI INCLUDED FOR ANALYSIS

Relationship	Alive (No.)	Number dead		Total
		Cancer death	Other death	
Paternal grandfathers ..	5	12	44	61
grandmothers ..	10	11	46	67
Maternal grandfathers ..	11	11	48	70
grandmothers ..	14	17	43	74
Fathers	48	22	59	129
Fathers' brothers ..	63	12	20	95
sisters	51	13	28	92
Mothers	72	13	52	137
Mothers' brothers ..	47	10	56	113
sisters	64	15	32	111
Brothers	153	4	32	189
Sisters	151	9	31	191
Totals	689	149	491	1329

occurring in these relatives were determined and compared with the number of such deaths expected using cohort mortality rates from tables in *Cancer Statistics for England and Wales* (Case and Pearson, 1957); the method of years at risk was used to calculate expected numbers of such deaths. Since lymphomas and leukaemias were not included in the Case-Pearson tables heading 'All cancers', expected numbers for these causes were calculated from the mortality rates for England and Wales for 1965, applied over the whole range. The period at risk for each individual was taken as his whole life span up to his age at the end of 1972, or at death. This was done because of the virtual impossibility of deciding for each individual a suitable age at which a period at risk should start. (One method of attacking this problem is that of Macklin, 1959.) Cancer deaths at early ages are of course small in number, so that the overall effect will not much increase the expectation, but what effect it does have is also such as to tend to reduce the magnitude of any excess of deaths observed from malignant disease. The Case-Pearson mortality rates are published only back to the quinquennium 1911-15. In the absence of evidence for any trends at the beginning of this century, however, the 1911-15 rates were applied to the years at risk before this. Statistical analysis of differences between numbers of cancer deaths observed and those expected was based upon the Poisson distribution.

RESULTS

The distribution of relatives with regard to their degree of relationship to the propositi and also the numbers alive or dying of cancer or other causes is shown in Table II.

When all cancer deaths are considered there was a significantly increased number of such deaths in relatives of patients with coeliac disease ($P < 0.001$). In male relatives there was an increased, although not significant, incidence of cancer deaths, but in female relatives the difference between observed and expected deaths was highly significant ($P < 0.01$) (Table III).

Comparison of observed and expected numbers of cancer deaths in male and female relatives in the various degrees of relationship to the propositi of each sex is shown in Table IV. This table shows an excess of cancer deaths in fathers of male propositi and in sisters and maternal grandmothers of female propositi. Taking all propositi together, there is also an excess of cancer deaths among

TABLE III
CANCER DEATHS IN ADULT COELIAC DISEASE
RELATIVES

Relatives	Number of cancer deaths		P
	Observed	Expected	
All	149	113.56	<0.001
Male	72	58.88	—
Female .. .	77	54.68	<0.01

fathers' siblings (brothers and sisters of the father of a proband) where 25 deaths were observed for an expectation of 13.78 ($P < 0.01$). In contrast the 25 deaths from cancer observed in mothers' siblings was not significantly different from the expectation (20.82).

Among male relatives the excess of cancer deaths could be attributed to three main sites, namely oesophagus ($P < 0.001$), bladder ($P < 0.01$), and brain ($P < 0.001$) (Table V). The remaining sites showed no significant differences either for individual sites or overall. When deaths from cancer at the three specific sites were examined further according to their relationship to the proband there was a statistically significant excess of deaths from bladder cancer in fathers (three deaths observed and 0.53 expected, $P < 0.05$), from oesophageal cancer both in male siblings of fathers (three deaths observed and 0.19 expected, $P < 0.001$) and in maternal grandfathers (three deaths observed and 0.48 expected, $P < 0.05$), and lastly from brain tumours in fathers' siblings

(three deaths observed, 0.03 expected, $P < 0.001$).

In female relatives the only individual site to show a significant excess was breast for which more than twice the expected number was observed ($P < 0.01$), but in this case the sum of remaining sites also showed a significant excess. The 15 deaths from unknown primaries certainly contribute to the excess but whether their re-allocation to specific sites would have brought to light any further associations could not of course be determined. More cancer deaths occurred than expected in each degree of relationship among the female relatives although such excess deaths achieved statistical significance in only one relationship, namely in female siblings of mothers (six deaths observed and 1.46 expected $P < 0.01$).

Among the 13 'coeliac' families, four families (30.8%) had more than one cancer death. Among all the families, 41 (29.5%) had more than one cancer. With these small numbers we could detect no difference.

DISCUSSION

Any study which relies heavily upon information from proband is open to bias but as far as is possible we believe we have minimized such errors. For example, since reliable information concerning the age and cause of death of many grandparents was not available for more than half of them, only 272 out of 556 were included in the analysis.

TABLE IV
CANCER INCIDENCE AMONG RELATIVES ACCORDING TO SEX OF PROBAND

Relatives	Male			Female			Total		
	Expected	Observed	P	Expected	Observed	P	Expected	Observed	P
Male									
Paternal grandfather	4.61	4	—	5.60	8	—	10.21	12	—
Maternal grandfather	5.29	4	—	5.46	7	—	10.75	11	—
Father	6.28	14	<0.01	7.51	8	—	13.79	22	<0.05
Father's brothers	3.26	6	—	3.50	7	—	6.76	13	<0.05
Mother's brothers	3.67	2	—	7.31	8	—	10.98	10	—
Brothers	1.95	0	—	4.44	4	—	6.39	4	—
Total	25.06	30	—	33.82	42	—	58.88	72	—
Female									
Paternal grandmother	4.85	3	—	5.50	8	—	10.35	11	—
Maternal grandmother	4.49	3	—	6.68	14	<0.01	11.17	17	—
Mother	5.12	5	—	6.59	8	—	11.71	13	—
Father's sisters	2.83	6	—	4.19	6	—	7.02	12	—
Mother's sisters	4.20	7	—	5.64	8	—	9.84	15	—
Sisters	1.59	1	—	3.00	8	<0.05	4.59	9	<0.05
Total	23.08	25	—	31.60	52	<0.001	54.68	77	<0.01

TABLE V
CANCER DEATHS IN ADULT COELIAC DISEASE RELATIVES BY PRIMARY SITE

Males (657)						Females (672)					
Site			Observed	Expected	P	Site			Observed	Expected	P
Oesophagus	..	..	9	2.23	<0.001	Breast	..	..	22	10.79	<0.01
Bladder	..	..	7	2.21	<0.01	Stomach	..	..	11	7.47	—
Brain	..	..	4	0.24	<0.001	Large bowel	..	..	11	11.72	—
Lung	..	..	18	13.70	—	Uterus	..	..	7	6.45	—
Stomach	..	..	12	10.40	—	Lymphoma	..	..	2	1.22	—
Large bowel	..	..	11	10.08	—	Lung	..	..	3	24	17.03
Prostate	..	..	2	3.63	—	Oesophagus	..	..	3		
Lymphoma	..	..	2	1.80	—	Tongue	..	..	1		
Pancreas	..	..	1	7	14.59	Kidney	..	..	1		
Skin	..	..	1			Pancreas	..	..	1		
N/D	..	..	5			N/D	..	..	15		
Totals	..	..	72	58.88	—	Totals	..	..	77	54.68	<0.01

Notes:

- 1 Expected numbers of cancer deaths have been determined separately only for the more commonly occurring primary sites
- 2 Cancer of colon and rectum are included under large bowel
- 3 N/D refers to relatives known to have died of cancer but in whom the primary site was not accurately determined

In seeking an explanation for our observed excess of cancer deaths in relatives of coeliac patients, four possibilities need to be considered.

1. The increased incidence of cancer deaths could be due to the fact that the probands were better able to recall details of relatives dying of cancer than dying of other causes. Indeed, Hagstrom and Ho (1972) showed that recollection for other cancers in the family members may be enhanced if the proband has cancer in comparison with control probands who do not. However, only six of the probands in this study had cancer, and in the remainder particular care was taken not to place undue emphasis upon cancer as a cause of death, not only for this reason, but also to avoid engendering anxiety.
2. The increased incidence of cancer deaths may be related to a family liability to cancer which is independent of the liability to coeliac disease. Indeed, some time ago, Warthin (1913) concluded that 'a marked susceptibility to carcinoma exists in certain families'. Lynch and his colleagues (Lynch and Krush, 1967; Lynch, Krush, and Larsen, 1967) suggested that such 'family cancers' tend to occur at an earlier age in succeeding generations, that multiple sites are a feature, that adenocarcinoma is prominent, and that an autosomal dominant pattern of inheritance may be operative. Lynch, Guirgis, and Albert (1974) have subsequently shown that a familial link for cancer can be demonstrated in

female relatives (who develop a breast tumour before the age of 55 years) of probands in whom there is no evidence of cancer, although Macklin (1959) considered that this familial pattern occurred only in relatives of breast cancer probands. For probands with tumours other than breast and for a series with no known tumour no familial aggregation could be demonstrated.

In the present study it has not been possible to assess the relevance of all these factors but the excess of breast cancer deaths could be the result of the familial nature of the series rather than the effect of a common predisposing factor.

3. Another source of bias which should be considered is the use of national death rates for what is primarily a regional sample. Although the Birmingham region is fairly representative of the country as a whole, some sites of cancer do show regional differences. Such an effect would of course be environmental in origin rather than genetic and the excess of bladder cancer that we found in relatives might be attributable to this cause.
4. The excess of cancer deaths may merely reflect an increase of tumours which are the sequelae of undetected coeliac disease in relatives. If this were the case then the pattern of tumours in relatives might be expected to mirror that of the coeliac patients themselves—that is, to show an excess of lymphomas and cancer of the oesophagus. The latter has

indeed been found to be in excess in relatives ($P < 0.001$), but only two deaths from lymphoma were recorded among male relatives and two in female for expectations of 1.80 and 1.22 respectively, and neither difference is statistically significant.

The question remains, therefore, whether the observed number of lymphomas is a true reflection of the frequency of their occurrence in relatives. It is possible that such tumours are under-reported. Thus coeliac patients, being under close medical supervision, are more likely to come to autopsy than would their relatives with undiagnosed disease. It is also possible that some of the unknown primaries in our series were in fact lymphomas which, in the early years of the survey, might not have been clearly diagnosed or, more likely, that such a diagnosis would have been more difficult for the layman to interpret as a malignant condition. Lastly the estimate of 10% of relatives with undiagnosed disease means that the susceptible subpopulation is well diluted by the rest of the series in which case it may be difficult to establish an excess of lymphomas in this situation.

In summary, our analysis has not detected any general increase in deaths from cancer at all sites. At present it is not possible to say with confidence if the excess of cancer at specific sites is due to a familial effect, either genetic or environmental but independent of coeliac disease, or whether it is the result of a small proportion of relatives with undiagnosed disease displaying an enhanced risk of certain cancers in a pattern similar to that in patients with established coeliac disease.

Requests for reprints: W. T. Cooke, MD, FRCP, General Hospital, Birmingham.

REFERENCES

- AUSTAD, W. I., CORNES, J. C., GOUGH, K. R., MCCARTHY, C. F., and READ, A. E. (1967). Steatorrhea and malignant lymphoma. The relationship of malignant tumours of lymphoid tissue and coeliac disease. *Amer. J. dig. Dis.*, **12**, 475.
- CASE, R. A. M. and PEARSON, J. T. (1957). Studies on Medical and Population Subjects No. 13. *Cancer Statistics for England and Wales, 1901 to 1955. (plus supplements from Chester Beatty Institute, London)*. HMSO, London.
- FALCHUK, Z. M., ROSENTINE, G. N., and STROBER, W. (1972). Predominance of histocompatibility antigen HL-A 8 in patients with gluten sensitive enteropathy. *J. clin. Invest.*, **51**, 1602.
- GOUGH, K. R., READ, A. E., and NAISH, J. M. (1962). Intestinal reticulosis as a complication of idiopathic steatorrhea. *Gut*, **3**, 232.
- HAGSTROM, R. M. and HO, Y. C. (1972). Family cancers among cases of primary liver cancer. *Cancer*, **29**, 1264.
- HARRIS, O. D., COOKE, W. T., THOMPSON, H., and WATERHOUSE, J. A. H. (1967). Malignancy in adult coeliac disease and idiopathic steatorrhea. *Amer. J. Med.*, **42**, 899.
- LILLY, F., BOYSE, A. E., and OLD, L. J. (1964). Genetic basis of susceptibility to viral leukaemogenesis. *Lancet*, **2**, 1207.
- LYNCH, H. T., GUIRGIS, H., and ALBERT, S. (1974). Familial breast cancer in a normal population. *Cancer*, **34**, 2080.
- and KRUSH, A. J. (1967). Heredity and adenocarcinoma of the colon. *Gastroenterology*, **53**, 517.
- , —, and LARSEN, A. L. (1967). Heredity and multiple primary malignant neoplasm: six cancer families. *Amer. J. med. Sci.*, **254**, 322.
- MACDONALD, W. G., DOBBINS, W. O., and RUBIN, C. E. (1965). Studies of the familial nature of coeliac sprue using biopsy of the small intestine. *New Engl. J. Med.*, **272**, 448.
- MACKLIN, M. T. (1959). Comparison of the number of breast cancer deaths observed in the relatives of breast cancer patients and the number expected on the basis of mortality rates. *J. nat. Cancer Inst.*, **22**, 927.
- STOKES, P. L., ASQUITH, P., and COOKE, W. T. (1973a). Genetics of coeliac disease. *Clinics in Gastroenterology*, p. 547. Saunders, London.
- , —, HOLMES, G. K. T., MACKINTOSH, P., and COOKE, W. T. (1972). Histocompatibility (HL-A) antigens in adult coeliac disease. *Lancet*, **2**, 162.
- , —, —, —, and — (1973b). Inheritance and influence of HL-A antigens in adult coeliac disease. *Gut*, **14**, 627.
- WARTHIN, A. S. (1913). Heredity with reference to carcinoma. *Arch. intern. Med.*, **12**, 546.