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Cancer incidence and factors associated with malignancies in coeliac disease during long-term follow-up

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Abstract

Background: The increased risk of malignancies in coeliac disease is well recognised, but data on incidence and predisposing factors are scarce. Our aim was to determine cancer incidence and its prognostic factors in coeliac disease during a long-term follow-up.

Methods: The study cohort comprised all (n = 1460) coeliac patients diagnosed in Tampere University Hospital catchment area during the period 1960-2000. Demographic data (age, gender, decade of diagnosis) and coeliac disease characteristics (presenting symptoms, signs of malabsorption, severity of villous atrophy) were obtained from medical records, and patients were stratified into subgroups accordingly. Standardised incidence ratios (SIRs) compared to general population of the same area were calculated for malignancies altogether and according to stratifications.

Results: The overall risk of malignancy was not increased (SIR 0.97; 95% confidence interval (CI) 0.84-1.11). The risk of non-Hodgkin lymphoma was elevated (SIR 3.0; 1.88-4.54) but less so after ≥15 years of follow-up (SIR 1.75; 0.70-3.60). Screen-detected coeliac disease or malabsorption at diagnosis was not associated with increased risk of non-Hodgkin lymphoma. The increased risk of gastrointestinal malignancies (SIR 1.42; 95% CI 1.07-1.85), particularly that of stomach and liver cancers, was associated with females, coeliac disease diagnosis before year 1981 and dermatitis herpetiformis.

Conclusions: The overall risk of malignancy was not increased in any coeliac disease phenotype. The risk of non-Hodgkin lymphoma was increased but not in screen-detected coeliac disease.

1 | INTRODUCTION

Diarrhoea and malabsorption are well-known symptoms in coeliac disease, but presenting symptoms are diverse. Coeliac patients are increasingly diagnosed due to extraintestinal manifestations such as dermatitis herpetiformis, arthralgia and neurological symptoms or detected by screening risk groups with mild or even no coeliac symptoms at all, especially subjects with family history of coeliac disease or with autoimmune diseases.[1] Coeliac disease is provoked by ingestion of gluten-containing cereals in genetically predisposed individuals. The resulting small intestinal mucosal damage recovers on a life-long gluten-free diet.[2] According to serological screening studies, coeliac disease affects approximately 1%-2% of population in Western countries.[3]

Diagnosed coeliac disease has been associated with increased risk of malignancies, especially with non-Hodgkin lymphoma and adenocarcinoma of the gastrointestinal tract.[4-13] Male gender, older age at coeliac disease diagnosis and classical coeliac disease phenotype with diarrhoea and weight loss have been suggested as possible risk factors, especially for developing refractory coeliac disease and subsequently non-Hodgkin lymphoma.[14-18] Conversely, the overall risk of malignancies in screen-detected coeliac disease has not been reported to be increased in most studies but the data are controversial.[12,19,20] Childhood coeliac disease has not been associated with an increased risk of lymphoma or other malignancies [5,10] although studies on this subject are scarce. Reports on whether gluten-free diet has a protective effect against malignancies are inconsistent.[16,21,22] Otherwise, data on risk factors for coeliac disease-associated malignancies are mostly lacking.

The aim of our study was to assess the relative risk and risk factors of malignancies in coeliac disease, focussing on coeliac disease phenotype at the time of diagnosis. We scrutinised a well-defined cohort of coeliac patients collected prospectively between 1960 and 2000 with a long-term follow-up of altogether 37 years.

2 | METHODS

2.1 | Study population

All patients diagnosed with coeliac disease at the Tampere University Hospital catchment area between January 1960 and December 2000 were prospectively included in the cohort. Approximately 16% of the Finnish population reside in Tampere University Hospital catchment area. The prevalence of coeliac disease in the area is slightly higher (0.7%) than that in Finland in general (0.6%).[23] The diagnoses were based on histological verification according to approved guidelines; duodenal villous atrophy and crypt hyperplasia (compatible with Marsh-Oberhuber 3 morphology[24,25]) in coeliac disease, and granular IgA deposits of the dermal papillae of the skin in direct immunofluorescence assay in dermatitis herpetiformis. The histological evaluations mainly took place in our department and ambiguous findings were scrutinised in multidisciplinary meetings. The date of duodenal or skin biopsy was set as the date of diagnosis. For those dermatitis herpetiformis patients clinically diagnosed before immunofluorescence assay became available in the 1980s, but whose diagnosis in each case was confirmed with the test later when it became available, the date of diagnosis was taken to be the date of clinical diagnosis. Duodenal biopsy was performed to 87% of dermatitis herpetiformis patients and 32% of them had normal villous architecture.

2.2 | Review of medical files and stratification

The medical records of the cohort were reviewed retrospectively in 2015 and individual data on patients, coeliac disease characteristics and the use of gluten-free diet were obtained when available. Eighty-eight records of deceased patients were no longer found. The cohort was stratified (Table 1) according to sex, age at (<20, 20-39, 40-59 and ≥60 years) and decade of (≤ 1980, 1981-1990, 1991-2000) coeliac disease diagnosis. Follow-up was stratified according to time since diagnosis (<2, 2-4.9, 5-14.9 and ≥15 years). The cohort was classified into four phenotype groups based on the presenting symptoms: 1) gastrointestinal symptoms, 2) malabsorption and weight loss, 3) dermatitis herpetiformis, 4) other extraintestinal symptoms and individuals detected by serologic screening in risk groups. Each patient was assigned to only one phenotype group according to the most prominent presenting manifestation. Gastrointestinal symptoms group contained patients presenting with diarrhoea, abdominal pain, reflux or obstipation. Malabsorption and weight loss category included patients with weight loss, anaemia or deficiency of iron, cobalamin, folic acid or calcium either alone or in combination. The dermatitis herpetiformis group included all patients presenting with a typical rash and immunofluorescence finding. Other extraintestinal symptoms (n = 196) included osteoporosis, infertility, neurological manifestations, arthralgia and childhood growth retardation. Screen detected group (n = 153) contained individuals with coeliac disease in the family or with an autoimmune disease (eg type 1 diabetes, autoimmune thyroiditis, arthralgias or IgA nephropathy). The whole cohort was stratified according to degree of small bowel villous atrophy at diagnosis. The damage was rated to be severe in cases of total or subtotal villous atrophy (corresponding Marsh-Oberhuber 3b-c), mild in case of partial villous atrophy (corresponding Marsh-Oberhuber 3a) and normal when no villous atrophy was found (corresponding Marsh 0-2). The response to gluten-free diet was considered to be achieved when villous atrophy was alleviated in follow-up biopsies. Patients showing no histological villous improvement as well as patients not adhering to gluten-free diet at all were assigned to the 'no response' group. In case of multiple control biopsies during the follow-up, the response was determined according to the best villous recovery achieved. The occurrence of non-Hodgkin lymphomas was evaluated case by case in relation to presenting symptoms.

TABLE 1 Characteristics of the study cohort

Variable (n = number of cases included in analyses)	n (%)
Sex (n = 1,460)	
Female	916 (63%)
Male	544 (37%)
Age at diagnosis (n = 1,460)	
<20 years	294 (20%)
20-39 years	492 (34%)
40-59 years	498 (34%)
≥60 years	176 (12%)
Year of diagnosis (n = 1,460)	
–1980	248 (17%)
1981-1990	601 (41%)
1991-2000	611 (42%)
Presenting phenotype (n = 1,372)[a,c]	
Gastrointestinal	454 (33%)
Malabsorption and weight loss	234 (17%)
Dermatitis herpetiformis	335 (24%)
Other extraintestinal, screen detected	349 (25%)
Degree of villous atrophy at diagnosis (n = 1,328)[b,d]	
Subtotal or total villous atrophy	898 (68%)
Partial villous atrophy	337 (25%)
Normal[b]	93 (7%)
Response to gluten-free diet (n = 938)[a,c,d]	
Yes	849 (91%)
No	89 (10%)
Follow-up (n = 1,460)	
0-1.9 years	13 (1%)
2-4.9 years	28 (2%)
5-14.9 years	147 (10%)
≥15 years	1272 (87%)

[a]Patients with missing data were excluded from the analysis.

[b]Normal villous architecture was detected in 93 patients with dermatitis herpetiformis.

[c]Non-responder = no villous improvement in control biopsy or non-compliant to gluten-free diet.

[d]Patients with missing data were excluded from analyses in each strata in stratified analyses.

2.3 | Malignancy data

The Finnish Cancer Registry maintains national registry of all cancers diagnosed since 1953. Since 1961 it has been compulsory for physicians and pathologists to report cancers diagnosed and the registry covers more than 98% of all diagnosed malignancies.[26] Malignancies are classified according to the International Classification of Diseases for Oncology, the third edition (ICD-O-3) since 2007, and data prior to 2007 have been converted to ICD-O-3. In the registry, small intestinal cancers included adenocarcinoma, carcinoid tumour and stromal tumour, whereas enteropathy-associated T-cell lymphoma (EATL) was categorised under non-Hodgkin's lymphoma. All Finnish residents have a unique identity code and these codes of the patients in our cohort were linked to the Finnish Cancer Registry to obtain data on malignancies.

2.4 | Statistical analysis

Concerning cancer incidence this was a prospective follow-up study while the risk factors for malignancy were analysed in a retrospective manner. The follow-up went from 1 January 1978 for patients who received their diagnoses before 1978 and for the rest from the date of diagnosis. The follow-up continued until death, date of emigration, or 31 December 2014, whichever occurred first. All cancers that were found before coeliac disease diagnosis was established were excluded. The expected numbers of malignancies were calculated by multiplying the observed person-years of follow-up by the incidence of each malignant disease in the respective sex, age and calendar period in the population of the Tampere University Hospital catchment area. The ratios of observed-to-expected cancers, the standardised incidence ratios (SIRs), were calculated for different malignancies altogether and according to stratifications and exact 95% confidence intervals (CI) were defined assuming that the numbers observed followed Poisson distribution. Basal cell carcinoma and precancerous lesions of breast, cervix and ovary were not included in the analysis of overall risk of malignancy. In stratified analyses, patients with missing data were excluded from analyses in each strata.

2.5 | Ethics

Data permits were granted by the National Institute for Health and Welfare (THL/1678/5.05.00/2016), Digital and Population Data Services Agency (VRK/44752/2017-3) and Tampere University Hospital Science Center (R15570). According to the Finnish legislation, no informed consent or approval by an ethics committee is required for registry-based studies when study populations are not contacted.

3 | RESULTS

Basic characteristics of the cohort are presented in Table 1. The coeliac cohort included 1,460 patients (63% female). Median age at coeliac disease diagnosis was 38 years (range 0.6-84.7) and median follow-up time 24 years (range 0-37), constituting 34,073 patient-years of follow-up. The follow-up was more than 15 years for 87% of patients. Gastrointestinal symptoms were the most frequent manifestation. Severe atrophy was detected in two thirds of patients with known villous atrophy severity (94% of patients) at the time of diagnosis. In 88 patients the severity of villous atrophy was not available and in 44 dermatitis herpetiformis patients (3% of all patients) no

TABLE 2 Standardised incidence ratios (SIRs) with 95% CIs for malignancies, by type of malignancy and time since the diagnosis of coeliac disease

			Time since the diagnosis of coeliac disease diagnosis (years)				
Malignancy	O	E	Total 35,073 person-years SIR (95% CI)	0-1.9 2,614 person-years SIR (95% CI)	2-4.9 4,032 person-years SIR (95% CI)	5-14.9 13,392 person-years SIR (95% CI)	≥ 15 14,035 person-years SIR (95% CI)
Any malignancy[a]	197	202.85	0.97 (0.84-1.11)	1.44 (0.77-2.46)	1.14 (0.68-1.80)	1.00 (0.78-1.26)	0.89 (0.72-1.08)
Lymphoproliferative diseases	26	16.34	1.59 (1.04-2.33)	5.24 (1.43-13.41)	2.33 (0.48-6.79)	1.80 (0.86-3.31)	1.03 (0.47-1.95)
Non-Hodgkin lymphoma	22	7.33	3.00 (1.88-4.54)	13.03 (3.55-33.35)	3.70 (0.45-13.36)	3.62 (1.66-6.87)	1.75 (0.70-3.60)
Hodgkin lymphoma	1	0.97	1.03 (0.03-5.75)	0.00 (0.00-54.64)	0.00 (0.00-34.58)	0.00 (0.00-9.80)	2.39 (0.06-13.32)
Gastrointestinal cancer	54	37.98	1.42 (1.07-1.85)	1.15 (0.14-4.14)	1.34 (0.36-3.42)	1.24 (0.71-2.00)	1.57 (1.08-2.22)
Oesophagus	3	1.75	1.72 (0.35-5.02)	0.00 (0.00-46.16)	0.00 (0.00-26.83)	1.69 (0.04-9.40)	2.14 (0.26-7.71)
Stomach	11	5.76	1.91 (0.95-3.41)	5.05 (0.61-18.24)	0.00 (0.00-5.82)	2.36 (0.77-5.50)	1.53 (0.42-3.92)
Small intestine	1	0.64	1.55 (0.04-8.64)	0.00 (0.00-148)	0.00 (0.00-84.92)	0.00 (0.00-17.27)	2.76 (0.07-15.37)
Colon	14	11.04	1.27 (0.69-2.12)	0.00 (0.00-8.10)	1.24 (0.03-6.89)	1.35 (0.44-3.15)	1.32 (0.57-2.59)
Rectum	9	7.19	1.25 (0.57-2.37)	0.00 (0.00-11.95)	1.88 (0.05-10.46)	1.23 (0.25-3.58)	1.28 (0.42-2.98)
Liver[b]	7	2.38	2.94 (1.18-6.04)	0.00 (0.00-45.11)	0.00 (0.00-24.88)	2.63 (0.32-9.48)	3.59 (1.17-8.37)
Pancreas	7	6.26	1.12 (0.45-2.30)	0.00 (0.00-14.04)	4.32 (0.52-15.58)	0.00 (0.00-1.76)	1.45 (0.47-3.38)
Lung	9	15.59	0.58 (0.26-1.09)	1.13 (0.03-6.28)	0.00 (0.00-2.55)	0.73 (0.20-1.87)	0.51 (0.14-1.31)
Renal	6	5.98	1.00 (0.37-2.18)	0.00 (0.00-12.90)	2.04 (0.05-11.39)	1.45 (0.30-4.24)	0.64 (0.08-2.29)
Bladder	4	6.26	0.64 (0.17-1.63)	0.00 (0.00-13.11)	2.06 (0.05-11.46)	0.00 (0.00-1.76)	0.88 (0.18-2.57)
Breast	27	39.36	0.69 (0.45-0.99)	1.16 (0.14-4.17)	1.30 (0.35-3.33)	0.77 (0.39-1.38)	0.49 (0.24-0.90)
Ovarian	2	4.47	0.45 (0.05-1.61)	0.00 (0.00-15.72)	0.00 (0.00-9.01)	0.60 (0.02-3.35)	0.46 (0.01-2.56)
Prostate	27	28.43	0.95 (0.63-1.38)	0.00 (0.00-4.00)	1.08 (0.13-3.90)	1.17 (0.58-2.08)	0.86 (0.47-1.44)
Skin, melanoma	3	6.89	0.44 (0.09-1.27)	3.64 (0.09-20.29)	0.00 (0.00-7.76)	0.44 (0.01-2.45)	0.26 (0.01-1.44)

Abbreviations: CI, confidence interval; E, Expected; O, Observed.

[a]Basal cell carcinoma (52 observed cases; SIR 1.19; CI 0.89-1.55) excluded.

[b]Cholangiocarcinoma and gallbladder cancer not included.

TABLE 3 Characteristics of patients with non-Hodgkin lymphomas of the gastrointestinal tract

N:o	Gender	Dg	Year of CD dg (age)	Year of NHL dg	Time from CD to NHL, years	Primary organ	Histology of NHL	Year of death
1	M	DH	1967 (16)	1999	28.8	Stomach	DLBCL	2018
2	M	DH	1972 (30)	1979	9.0	Colon, mesenterium	Diffuse	Alive
3	F	CD	1987 (58)	1994	7.4	Ileum	EATL	1995
4	M	CD	1989 (65)	1992	3.0	Jejunum	EATL	1997
5	M	CD	1990 (50)	2001	10.9	Jejunum	T-cell	2013
6	F	CD	1994 (53)	1995	0.4	Jejunum	Centroblastic	1999
7	M	CD	1996 (57)	1996	0.2	Ileum	EATL	1996
8	M	DH	1996 (58)	2002	6.0	Jejunum	EATL	2007
9	M	CD	1997 (45)	1997	0.1	Intestine	T-cell	1997
10	F	CD	1998 (69)	1999	0.5	Jejunum	T-cell	2000

Abbreviations: CD, coeliac disease; DH, dermatitis herpetiformis; DLBCL, diffuse large B-cell lymphoma; EATL, enteropathy-associated T-cell lymphoma; NHL, non-Hodgkin lymphoma.

duodenal biopsy was performed at diagnosis. A response to gluten-free diet was observed in 90% of patients after a median of 1.9 years (range 0.1-41 years). The response could not be assessed in 522 patients mainly due to missing data on implementation of gluten-free diet or on villous atrophy severity in either diagnostic or control biopsy. Normalisation of villous architecture was accomplished in 77% of patients, while mild and severe villous atrophy persisted in 17% and 5% of patients respectively.

Altogether 227 cancers occurred in 213 coeliac patients. As this was a prospective follow-up study, the 30 cancers that were found before coeliac disease diagnosis was established were excluded. The origins of these cancers were highly variable (16 different cancers including two small bowel EATLs) (Table S1). Among patients with and without data on response, 128 (13.6%) and 70 (13.4%) incident cancers were detected respectively. In the entire follow-up time, the overall risk of malignancy was similar to that in general population (SIR 0.97; 95% CI 0.84-1.11) (Table 2). The risk of non-Hodgkin lymphoma was increased (SIR 3.00; 1.88-4.54), being most prominent within 2 years of coeliac disease diagnosis (SIR 13.03; 3.55-33.35), but after over 15 years of follow-up the increase was lower and no longer significant (SIR 1.75; 0.70-3.60). Ten of the 22 non-Hodgkin lymphomas detected affected the gastrointestinal tract including four EATLs, three T-cell lymphomas in which specific histology was no longer retrievable and three B-cell lymphomas (Table 3). The risk of gastrointestinal cancers as a whole was elevated (SIR 1.42; 1.07-1.85), this increase depending mainly on the occurrence of stomach and hepatic cancers (Table 2). The only observed small bowel cancer was a gastrointestinal stromal tumour (GIST). The overall risk of breast cancer was lower than that in the population (SIR 0.69; CI 0.45-0.99); this positive effect was obtained especially after ≥15 years of follow-up. Basal cell cancer was not included in the assessment in the principal analysis of malignancy risk, but SIR for this skin cancer was at the population level (SIR 1.19; 0.89-1.55).

In stratified analysis, no potential risk factors were associated with the overall risk of malignancy (Table 4). The risk of non-Hodgkin lymphoma was not increased in patients (n = 234) presenting with malabsorption, weight loss or both at the time of diagnosis (SIR 0.90; 0.02-4.99). Also, no cases of lymphoma occurred among coeliac patients detected by serological screening in risk groups. Conversely, the risk of non-Hodgkin lymphoma was increased in all other phenotypes and in all patients diagnosed with coeliac disease at ≥20 years of age. In patients diagnosed with coeliac disease at the age of <20 years, the relative risk (SIR 7.58) was even higher (based on two detected non-Hodgkin lymphomas at ages 47 and 48 years), but the confidence intervals were wide between the limits and the elevation was thus not statistically significant. Each of these two non-Hodgkin lymphoma cases had lapses in maintaining gluten-free diet. The SIR of gastrointestinal malignancies was highest in female gender, coeliac disease detected before 1981 or with those presenting with dermatitis herpetiformis (Table 4). Considering specific gastrointestinal malignancies, a statistically significant increased risk of primary liver cancer was observed in females (SIR 3.75; 1.02-9.60), in patients diagnosed with coeliac disease at age 40-59 years (SIR 5.18; 1.07-15.14) and in those with a follow-up of ≥15 years (SIR 3.59; 1.17-8.37). Contributory factors to cancer development (hepatitis C, non-alcoholic steatohepatitis, primary biliary cholangitis and alcohol consumption) were noted in four of seven cases. The risk of stomach cancer was apparent in females (SIR 2.78; 1.20-5.47), in patients diagnosed with coeliac disease at age 20-39 years (SIR 5.34; 1.10-15.61) and in patients presenting with dermatitis herpetiformis (SIR 2.85; 1.04-6.19). Seven of 11 stomach cancer patients had either *Helicobacter pylori* infection (n = 3), atrophic gastritis (n = 3) or history of gastric resection (n = 1) as a possible predisposing factor.

4 | DISCUSSION

In this follow-up study of coeliac disease patients followed up for a median of 24 years, the overall cancer incidence was not increased in any phenotype based on presenting symptoms or at any time

TABLE 4 Standardised incidence ratios (SIRs) with 95% confidence intervals (CI) for malignancies, non–Hodgkin lymphomas and gastrointestinal malignancies among coeliac disease (CD) patients according to potential risk factors

Risk factor	Any malignancy[a] SIR (95% CI)	Non-Hodgkin lymphoma SIR (95% CI)	Gastrointestinal malignancies SIR (95% CI)
Sex			
Female	0.97 (0.80-1.15)	2.57 (1.28-4.59)	1.64 (1.13-2.28)
Male	0.98 (0.78-1.21)	3.61 (1.80-6.46)	1.16 (0.71-1.79)
Age at CD diagnosis			
<20 years	0.55 (0.11-1.59)	7.58 (0.92-27.37)	0.00 (0.00-6.28)
20-39 years	0.97 (0.71-1.28)	3.36 (1.23-7.31)	1.68 (0.87-2.93)
40-59 years	1.00 (0.82-1.19)	2.38 (1.09-4.52)	1.41 (0.94-2.04)
≥60 years	0.97 (0.70-1.30)	3.33 (1.08-7.76)	1.32 (0.73-2.25)
Year of CD diagnosis			
1980 or earlier	0.97 (0.71-1.31)	3.77 (1.38-8.19)	2.07 (1.23-3.27)
1981-1990	0.99 (0.79-1.22)	2.23 (0.90-4.58)	1.10 (0.65-1.74)
1991-2000	0.95 (0.74-1.19)	3.47 (1.59-6.59)	1.39 (0.82-2.19)
Presenting phenotype at diagnosis			
Gastrointestinal	0.93 (0.71-1.20)	3.13 (1.26-6.45)	0.98 (0.49-1.75)
Malabsorption	0.97 (0.65-1.38)	0.90 (0.02-4.99)	1.96 (0.98-3.51)
Dermatitis herpetiformis	1.04 (0.80-1.32)	3.99 (1.82-7.57)	1.73 (1.09-2.62)
Extraintestinal or screen detected	0.96 (0.67-1.33)	3.71 (1.20-8.64)	1.25 (0.54-2.46)
Degree of villous atrophy at diagnosis			
Subtotal or total atrophy	0.87 (0.71-1.06)	2.66 (1.33-4.76)	1.28 (0.84-1.87)
Partial atrophy	0.98 (0.72-1.29)	3.95 (1.59-8.14)	1.33 (0.68-2.31)
Normal	1.04 (0.66-1.54)	2.56 (0.31-9.23)	1.67 (0.72-3.28)
Response to gluten-free diet[b]			
Yes	0.95 (0.76-1.15)	2.17 (0.94-4.27)	1.64 (1.11-2.34)
No	1.29 (0.72-2.12)	2.36 (0.06-13.13)	1.81 (0.49-4.64)

Abbreviation: CI, confidence interval.

[a]Basal cell carcinoma excluded from the analysis of overall risk of malignancy.

[b]Non-responder = no villous improvement in control biopsy or non-compliant to gluten-free diet.

during the follow-up. The increased overall risk of non-Hodgkin lymphoma declined over time. The risk of non-Hodgkin lymphoma was increased in patients presenting with gastrointestinal symptoms and dermatitis herpetiformis but not in patients suffering from malabsorption and weight loss or diagnosed through screening.

With regard to overall cancer incidence, our finding differs from most other studies involving coeliac patients diagnosed during the same time period as the present cohort.[4,5,7,10] A few other studies reported similar risk estimate as us [8,27]; in one study only the post-diagnostic period was included in the risk-estimate [27] and in another the confidence intervals were relatively wide.[8] Our risk-estimate for non-Hodgkin lymphoma was within the range (two to sevenfold) reported previously.[8-12,14,27-30] During the follow-up, the risk declined and disappeared after ≥15 years of follow-up. It can be speculated that good compliance with gluten-free diet had an impact to the better results, even though we were not able to show the positive effect of the diet in the present survey. We were not able to evaluate adherence to the diet in individual cases, but as many as 91% of our patients achieved response in duodenal control biopsy indicating that the overall compliance was good, which again indicates that gluten-free diet would have a protective effect against malignancy. It is noteworthy that compliance or response has not been reported in the many other studies.[4,5,7,10] The data on response were missing in 522 patients, mostly because control biopsies were performed after transmission of follow-up to primary health care. It can be speculated whether these patients were engaged to coeliac disease treatment and how did it affect the estimation of cancer risk. However, no difference was observed in the cancer rate between patients with (13.6%) and without (13.4%) data on response. Furthermore, it is important to note that the overall cancer incidence was not increased despite the increases in risk of non-Hodgkin lymphoma and gastrointestinal cancers. This is possibly explained by the low absolute

numbers of these cancers in conjunction with the decreased risk of breast cancer.

No association was observed between the risk of non-Hodgkin lymphoma and malabsorption and weight loss at the time of diagnosis. By contrast, Leslie et al [14] reported a relationship between weight loss at coeliac disease diagnosis and lymphoproliferative diseases (LPDs) (12.5% in coeliac disease with LPD and 4.0% in coeliac disease without LPD, $P = 0.028$) and Olen et al [16] showed increased risk of lymphoma in patients presenting with weight loss (OR 2.9) or having vitamin B12 deficiency (OR 5.2). The overall risk of non-Hodgkin lymphoma was sevenfold in the study of Leslie et al [14] (not reported by Olen et al [16]). Consistent with the present study, anaemia at diagnosis did not increase the risk of LPDs in these two studies.[14,16]

The relative risk of non-Hodgkin lymphoma was slightly higher in dermatitis herpetiformis patients than in the other phenotypes. In contrast, in Swedish [10] and British [5] studies, the risk was two to threefold higher in coeliac disease than in dermatitis herpetiformis. In the present series, the SIR of non-Hodgkin lymphoma was clearly highest among dermatitis herpetiformis patients diagnosed before 1981. The need for strict gluten-free diet in the treatment of dermatitis herpetiformis gained recognition after this, in the 1980s, which might explain the observed excess risk of non-Hodgkin lymphoma. Supporting this, Finnish dermatitis herpetiformis patients who contracted non-Hodgkin lymphoma were shown to adhere to gluten-free diet significantly less strictly than the patients without lymphoma.[31]

The elevated risk of gastrointestinal cancer was mainly due to excess of stomach and liver cancers in women. Moreover, the relative risk of stomach cancer was slightly increased among dermatitis herpetiformis patients. A recent review on the association of autoimmune diseases and stomach cancer reported a similar finding (RR 1.7) for dermatitis herpetiformis,[32] but other studies focussing specifically on the risk of malignancies in dermatitis herpetiformis found no increased risk.[5,10,33] Nevertheless, the number of these cancers observed was small in our cohort and no precise conclusions can thus be drawn. This issue requires further studies. Interestingly, opposite to the recent Swedish study,[34] we did not observe any small bowel adenocarcinomas.

We found a decreased risk of breast cancer; a similar conclusion has also been reported in several earlier studies.[5,7,10,11,27,28,35] A recent Swedish study showed an association between a genetic predisposition to coeliac disease and a decreased risk of breast cancer caused by shared polygenic variation of immune related regions.[36] Women with coeliac disease have similar fertility as the general female population but they give birth at an older age,[37] which may predispose to higher breast cancer risk. Conversely, a shorter reproductive period caused by delayed menarche and early menopause in women with coeliac disease may lower the risk.[5,11] Nevertheless, no definite explanation for this positive outcome has so far been proposed.

No gastrointestinal cancers occurred among coeliac patients diagnosed in childhood, whereas two non-Hodgkin lymphomas were found to have developed later in life (possibly influenced by lapses in maintaining gluten-free diet) in this patient group. These low numbers of both gastrointestinal and lymphatic malignancies were comparable with previous reports from Sweden and the United Kingdom.[5,10,12]

The main strength of our study was the large and prospectively assembled cohort of coeliac patients followed up for almost 40 years, allowing thus a plausible estimation of long-term cancer risk in coeliac disease. At the time our cohort was compiled, it included all coeliac disease cases diagnosed with a spectrum of clinical phenotypes in the Tampere University Hospital catchment area. Most of the diagnoses were established in our centre but follow-up was transferred to primary health care already 1 year after the diagnosis. Therefore, we believe that this series gives a more reliable picture of the true risk of malignancy than some earlier studies. We were able to obtain detailed individual information enabling assessment of the risk rate of malignancies occurring in different coeliac disease phenotypes. By contrast, other studies have mainly evaluated the malignancy risk in general, not focussing on different presentations.[7,10,11,27]

This study also had limitations. The data on coeliac disease characteristics were drawn from patient records, and all the desired information could not be retrieved. Moreover, it was not possible to assess the duration of coeliac disease symptoms prior to diagnosis and therefore the association between coeliac disease and the 30 excluded cancers could not be defined. Longitudinal assessment of the persistence of strict gluten-free diet was not possible. However, the observed response rate in duodenal control biopsies in our study was 91% indicating good adherence to gluten-free diet. The response rate is also in line with those reported in other Finnish studies assessing compliance with gluten-free diet and villous recovery.[2] Moreover, long-term compliance with gluten-free diet has been excellent in our Tampere coeliac disease and dermatitis herpetiformis cohorts—>93% [38] and 98% [39] respectively. These percentages involve by and large the same patient series as the present study. We had no information on confounding risk factors for malignancies such as alcohol and tobacco consumption.

In conclusion, we showed that the overall risk of malignancy was not increased in any coeliac disease phenotype even in long term. As to non-Hodgkin lymphoma, the risk was increased, but the excess declined over time. No significant risk was observed in patients with diagnosis of coeliac disease in childhood, with screen-detected coeliac disease or in those suffering from malabsorption at the time of diagnosis. Our findings suggest that coeliac disease-associated risk of malignancies is not increased in general, but variations in coeliac disease presentation may have an impact on prognosis. In order to focus surveillance to coeliac patients with an elevated risk of malignancy, prospective studies assessing the risk in different coeliac disease phenotypes are warranted.

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AUTHORSHIP STATEMENT

Guarantor of the article: Katri Kaukinen.

Specific author contributions: Inka Koskinen involved in study design, project coordination, review of the medical files, statistical analyses, interpretation of the data and writing of the article; Kaisa Hervonen and Timo Reunala involved in data collection and revision of the manuscript; Eero Pukkala involved in study design, statistical analyses and revision of the manuscript; Katri Kaukinen and Pekka Collin involved in study design, interpretation of the data and revision of the manuscript. All the authors have read and approved the final manuscript.

ETHICS STATEMENT

The authors confirm that the ethical policies of the journal, as noted in the journal's author guidelines page, have been adhered to and the appropriate data permits have been received. According to the Finnish legislation, no informed consent or approval by an ethics committee is required for registry-based studies when study populations are not contacted.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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