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Risk of lymphoproliferative malignancy in celiac patients with a family history of lymphoproliferative malignancy

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Abstract

Background and aims—Individuals with celiac disease (CD) are at increased risk of lymphoproliferative malignancy (LPM). We examined if a family history of LPM or any cancer influenced the risk of LPM in individuals with CD.

Methods—We identified 28,996 individuals with biopsy-verified CD (equal to villous atrophy, Marsh histopathology stage 3), of whom 616 had family history of LPM. Cox regression then estimated hazard ratios (HRs) for LPM in these 616 compared with two control groups. We also examined the risk of LPM in CD individuals with a family history of any cancer (n=8,439).

Results—During follow-up, 2/616 CD individuals with a family history of LPM, and 235/28,380 CD individuals without a family history of LPM developed LPM themselves. CD individuals with a family history of LPM were not at increased risk of LPM compared to general population controls (HR=1.18; 95%CI=0.27–5.10), or compared to CD individuals without a family history of LPM (adjusted HR=0.31; 95%CI=0.08–1.23). We found no increased risk of LPM in CD individuals with a family history of any cancer.

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Author contributions:

ICMJE criteria for authorship read and met: JFL, BL, AE, JAM, ART, PG.

Agree with the manuscript's results and conclusions: JFL, BL, AE, JAM, ART, PG

Designed the experiments/the study: JFL

Collected data: JFL

Analyzed the data: JFL

Wrote the first draft of the paper: JFL.

Contributed to the writing of the paper: AE, BL, JAM, ART, PG.

Contributed to design of study and interpretation of the data analyses: JFL, BL, AE, JAM, ART, PG.

Interpretation of data; approved the final version of the manuscript: JFL, BL, AE, JAM, ART, PG

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With the exception of JAM, all authors declare that they have no conflicts of interest and nothing to declare.

Conclusion—This study found no evidence that a family history of LPM or any cancer increases the risk of future LPM in individuals with CD. Despite the large number of study participants, this study is however limited by few positive events due to a low absolute risk of LPM even in individuals with CD.

Keywords

cancer; celiac; coeliac; lymphoma; lymphoproliferative; malignancy

Introduction

Celiac disease (CD) is a common immune mediated disorder occurring in approximately 1% of the Western population.[1, 2] It is triggered by gluten exposure in genetically susceptible individuals. Although a recent meta-analysis indicated that individuals with CD are at no increased overall risk of cancer,[3] there is strong evidence of a positive association between CD and lymphoproliferative malignancy (LPM).[4–11] LPM is currently one of the most commonly diagnosed malignancies in the US,[12] and exposure to certain autoimmune and chronic inflammatory conditions increases the risk for future LPM.[13]

Earlier studies on CD and LPM have found a 2- to 6 fold increased risk of LPM in CD.[4–11] The most plausible explanation for this excess risk is the chronic inflammation seen in CD, since there seems to be a relationship between degree of mucosal injury and LPM risk.[7] Other than degree of inflammation it is however possible that genetic factors play a role for the risk of LPM in CD.[14–18] For instance, Altieri *et al* reported that a having a parent with Non-Hodgkin Lymphoma (NHL), the dominating LPM in adults, increased risk of NHL 1.8-times, while having a sibling with NHL increased the risk by a factor 1.9.¹⁵ Another Swedish study reported that individuals who had a relative with Diffuse B-cell Lymphoma, were at ten times increased risk of having Diffuse B-cell Lymphoma.[18] Certain data also suggest that individuals who migrate from one country to another retain the lymphoma pattern of the ancestor country.[19]

Among the potential explanation for an increased risk of lymphoma in individuals with relatives of lymphoma are genetic mutations.[20]

Therefore we aimed to determine if a family history of LPM influences the future risk of LPM in individuals with CD. A secondary aim was to calculate the risk of LPM in individuals with CD and a family risk of any cancer.

Methods

Collection of data on CD

In 2006–2008, we collected data on individuals with CD through small intestinal biopsy reports.[21] The biopsies had been performed between 1969 and 2008 in Sweden's 28 pathology departments. We defined CD as having villous atrophy (VA; marsh histopathology stage 3).[22] We did not require a positive CD serology for the CD diagnosis but a validation of a random subset of individuals from our cohort has shown that 88% of those with available CD serology data, were positive at time of biopsy.[21]

Biopsy report data were obtained by IT technicians, who carried out searches for biopsy date, personal identity number,[23] morphology code (according to the Swedish SnoMed classification, please see the Appendix), and topography (duodenum or jejunum). Since we searched computerized biopsy databases, most individuals had received their CD diagnosis

in 1990 or later (Table 1). Additional data on the data collection have been published previously.[21]

For each individual with CD the government agency *Statistics Sweden* selected 5 reference individuals from the Total Population Register, matched for sex, age, calendar year and county. Only individuals without a prior record of small intestinal biopsy were eligible as controls.

Since we have used the matching procedure of the current study before, it means that our study population was at first identical to that of our study on mortality in CD (restricted to individuals with CD (n=29,096) and their matched controls (n=144,522)).[24] From this study sample, we then excluded individuals with a diagnosis of LPM before the date of CD diagnosis (n=100) or study entry in the matched controls (n=244). Since all analyses were performed stratumwise we excluded 253 controls whose matched individuals with CD had been excluded (e.g. due to a prior LPM diagnosis). All study participants were free from LPM at study start, and in total this study was based on 28,996 individuals with CD and 144,025 matched controls.

Swedish Cancer Register and cancer definitions

Cancer data were obtained from the Swedish cancer register.[25] This register started in 1958. Some 99% of malignancies are verified morphologically, and Swedish physicians are mandated to report newly diagnosed cancers to the register.[26] In a report from 2009, Barlow *et al* estimated that 96.3% of all cancers are reported to the register.[27] LPM was defined as having an ICD-7 code of 200–204. In a subanalysis we examined the risk of NHL (ICD7: 200, 202, 204.1) according to family history of cancer.

Follow-up

Follow-up time began on the date of biopsy with VA (equal to date of CD diagnosis), and the corresponding date in the matched controls. Follow-up time ended either with LPM diagnosis, death, emigration, or end of follow-up (December 31, 2009), whichever occurred first.

Family history of LPM or of any cancer

First-degree relatives (parents, siblings, offspring) of individuals with CD, as well as spouses were identified through the Swedish Multigeneration Register.[28] The Multigeneration register contains data on the personal identity number (PIN) of each index person, PIN and birthdate of father and mother, the child's position in the mother's family, date of immigration and adoption data, etc. As of December 2005, this register had information about 9,371,000 individuals. For those born in Sweden (7.7 million), there were data on the mother in 97% and on the father in 95%. The register contains data on index persons born from 1932 and later, and still alive on Jan 1, 1961. For individuals born 1947 or later, when the personal identity number was introduced, 98% have information on their biological mothers, a figure reaching 100% in those born 1961 or later.

We restricted siblings to individuals with the same mother and father as the index individual with CD, and excluded adopted siblings. We linked first-degree relatives (parents, siblings, offspring) of CD individuals to the Cancer Register. We also obtained data on cancer history in spouses. Spouses share the same environment as CD cases, but not the genetic background. Spousal analyses constitute an important contrast to the first-degree relatives analyses. An excess risk of LPM in CD individuals whose *parents, siblings or offspring* had a record of cancer, but not in CD individuals whose *spouses* had a record of cancer, would

strongly argue that genetic factors play a role for the excess LPM risk seen in the average patient with CD.[7, 11]

In all, 616 individuals with CD had a first-degree relative with LPM, and 8,439 had a first-degree relative with any cancer (spouses: 41 and 856 respectively). We only accepted family cancers taking place before the date of LPM diagnosis in the CD individual or end of follow-up for other reason. Restricting family history to LPM and any cancer occurring in the relative before the date of CD diagnosis of the index individual (and start of follow-up), 398 individuals had a family history of LPM and 5,557 a family history of any cancer.

Statistics

Our main outcome was the development of LPM in CD. We used an internally stratified Cox regression to calculate hazard ratios (HR) for future cancer. The internal stratification means that each stratum consisting of one index individual and his/her matched controls was analyzed separately before a summary HR was calculated.

First we examined the risk of cancer (LPM and in secondary analyses also “any cancer”), in CD individuals *with* a family history of LPM or any cancer compared to matched general population controls. We also estimated the risk of LPM in CD individuals *without* family history of LPM or cancer compared to general population controls. Similar analyses were carried out for CD individuals whose spouse had a history of cancer.

Then we compared the risk of LPM in CD individuals with family history of LPM vs. that of CD individuals without such family history (internal comparison), and likewise according to a family history of any cancer. Since CD individuals were not matched to each other, we adjusted the internal comparisons for age at CD diagnosis (10-year increments), sex, and calendar year at CD diagnosis (-1989, 1990–99, 2000-). In a final analysis we included family history for LPM (and any cancer) as a co-variate. In this analysis we considered family history for cancer in both CD individuals and their controls. We then tested the interaction term “CD*family history” to see whether the presence of a family history modified the association between CD and LPM risk. In this analysis, CD individuals and controls were matched on both birth year and age.

A description of the main analyses is given in Figure 1.

Subanalyses in CD individuals with a family history of any cancer

Due to limitations in power, subanalyses were only carried out in CD individuals with a family history of *any* cancer. In these analyses we stratified for age (0–19, 20–39, 40–59, 60 years or above), sex, and calendar period (-1989, 1990–1999, 2000-).

In a sub-analysis we adjusted for education. Education data (4 predefined categories) were missing in 4.0% of the study individuals. Individuals with missing data were fitted into a fifth category. In a separate analysis we also estimated HRs excluding the first year of follow-up.

P-values < 0.05 were regarded as statistically significant. Data analyses were performed using SPSS 20.

Ethics

The study was approved by the Research Ethics Committee in Stockholm, Sweden (June 14th, 2006).

Results

The majority of study participants were diagnosed in 1990 or later (Table 1). The median year of diagnosis of CD was 1998 in both those with a family history of LPM and those without such family history. Individuals without a family history of LPM were more often diagnosed with CD in childhood (Table 1), and the median age at CD diagnosis differed (family history of LPM: 44 years; and no family history: 30 years). Not considering family history of LPM, the HR for LPM in CD individuals compared to the general population, was 2.84 (95% CI=2.42–3.23).

Family history of LPM

Some 616 individuals with CD had a family history of LPM (of these 597 had one relative with LPM, 96.9%). During a follow-up of 7,605 person-years, 2 of these 616 individuals developed LPM corresponding to an incidence rate of 26/100,000 person-years (Table 2). This corresponded to a HR of 1.18, but confidence intervals were wide due to small numbers (95% CI=0.27–5.10) (Table 2 and Figure 1). Looking specifically at the risk of NHL, the HR was 2.16 (95% CI= 0.47–9.97). Due to the small number of positive events we abstained from any stratified subanalyses. As the 2 LPM cases occurred in CD individuals whose relatives had a record of LPM before CD diagnosis (n=398), the HR increased slightly when we restricted our analysis to family history before CD diagnosis (HR=1.60; 95% CI=0.36–7.08).

CD individuals with a family history of LPM were at no increased risk of future LPM compared to CD individuals without a family history of LPM (adjusted HR=0.31; 95% CI=0.08–1.23) (Table 3) (adjusted HR for NHL: 0.36; 95% CI=0.09–1.45). The lack of association with future LPM remained when we restricted our analyses to individuals with CD diagnosed in adulthood (data not shown), and after adjustment for education (data not shown).

Our interaction analysis found that family history of LPM did not modify the risk of LPM in individuals with CD ($p=0.403$).

Only 41 individuals with CD had a spouse with a record of LPM. None of these CD individuals developed LPM during the 462 years of follow-up, and hence no HR for LPM could be estimated.

Family history of any cancer

During a follow-up of 98,541 person-years, 60 of the 8,439 CD individuals with a family history of cancer developed LPM (Table 2).

Individuals with CD who had a family history of any cancer were at an increased risk of LPM compared to general population controls (HR=2.00; 95% CI=1.50–2.68) (Table 2) (with a HR for future NHL of 2.81; 95% CI=2.00–3.95). In total some 8,439 individuals with CD had a family history of cancer, out of which 6,396 (75.8%) had one relative with cancer, and the other 2,043 at least two relatives with any cancer. Subanalyses on LPM risk in CD according to age, sex and calendar period at CD diagnosis are given in Table 3.

CD individuals with a family history of any cancer were at a lower risk of future LPM compared to CD individuals without a family history of any cancer (adjusted HR=0.60; 95% CI=0.44–0.81) (Table 4) (adjusted HR for NHL: 0.60; 95% CI=0.40–0.79). Risk estimates were similar when we restricted our analyses to individuals with CD diagnosed in adulthood, or when we adjusted for age according to 5-year-increments instead of 10-year-increments. Adjustment for education did not influence the risk estimates (data not shown).

Our interaction analysis found that family history of any cancer did not modify the risk of LPM in individuals with CD ($p=0.090$).

Compared to general population controls, CD individuals whose spouse had a record of any cancer were at no increased risk of LPM ($HR=0.88$; 95%CI=0.37–2.09)(Table 2).

LPM risk according to family member with any cancer

Compared to general population controls, the HR for LPM in individuals with CD whose mother had a record of any cancer was 1.65 (95%CI=0.98–2.76), and slightly higher when the father had a cancer record ($HR=2.43$; 95%CI=1.57–3.76). Having a sibling ($HR=1.46$; 95%CI=0.78–2.17) or an offspring ($HR=1.60$; 95%CI=0.86–2.95) with a record of cancer yielded similar risk estimates.

Discussion

The main finding of this study was that a family history of LPM or any cancer does not seem to increase the risk of future LPM in individuals with CD. Neither does family history of LPM or any cancer seem to influence the risk of NHL in CD patients.

We are not aware of any previous study examining the role of family history of LPM or any cancer for the risk of future LPM in CD individuals. Overall, CD was associated with a 2.8-fold increased risk of LPM in our study. This is slightly higher than in two recent papers (Leslie *et al*[29]: standardized incidence ratio (SIR)=6.48; and Grainge *et al*[30]: SIR=5.82), potentially due to different source populations and different ascertainment of CD.

While, Gao *et al* found a small excess risk of NHL (odds ratio, OR=2.03; 95%CI=1.29–3.19) among siblings of individuals with CD, it should be noted that their study examined NHL risk according to family history of CD (while we looked at family history of LPM), their findings nevertheless suggest that genetic factors may influence the risk of future LPM.

Altieri *et al* reported a 2-fold increased risk of NHL in individuals whose parents or siblings had a record of NHL.[16] In a more recent paper by the International Lymphoma Epidemiology Consortium (InterLymph) consisting of more than 10,000 cases with NHL and 11,000 controls, the researchers found an elevated risk of NHL in individuals whose first-degree relatives had NHL (OR=1.5; 95%CI=1.2–1.9).[17] The risk of NHL was increased also in individuals with a family history of Hodgkin lymphoma or leukemia.[17] Still it should be noted that recent research on genetic risk factors in LPM suggests that individual LPM subtypes have different risk factors.[31] Due to limited power we were unable to examine the influence of LPM subtype on the risk of individual LPM subtypes in patients with CD.

Our study was based on more than 28,000 individuals with biopsy-verified CD, out of whom 616 had a family history of LPM and 8,439 had a family history of any cancer. The lack of positive association between family history of LPM and LPM risk in CD individuals may have several explanations. It is possible that CD individuals with a family history of LPM or any cancer adhere better to a gluten-free diet in order to avoid cancer. Of note, also individuals with CD whose spouse had a record of any cancer seemed to have a slightly lower risk of LPM. A recent Swedish case-control study indicated that dietary adherence could have a protective effect against LPM,[32] but data in this area is contradictory. While two recent studies of undiagnosed CD (US: older population[33]; and Italy: register-based study[34]) suggest that gluten exposure may not increase the risk of LPM, Finnish researchers have reported an increased risk of death from LPM [35] and of incident LPM[36] in individuals with positive endomysial antibodies (but not in those with positive

tissue transglutaminase antibodies). We are not aware of any study on the risk of incident LPM in CD from Britain, but a recent study based on the Cambridge General Practice Health Study found no evidence that undiagnosed CD (and thereby exposure to gluten) was associated with increased cancer mortality.[37] Unfortunately the current study did not have access to individual-based data on dietary adherence. In a subset of individuals undergoing patient chart validation, some 17% of CD individuals had indications of poor dietary adherence.[21] It is possible that CD individuals with a family history of LPM or any cancer had a different smoking pattern than the average individual with CD, resulting in a lower HR for LPM. Smoking is a risk factor for LPM.[38] Most studies suggest that CD is negatively associated with smoking.[39, 40]

We cannot rule out that there are false-negative CD patients in the control group, but given that they are unlikely to make up more than about 1% of all controls this should not affect our risk estimate.

Finally, despite our nationwide study design and the occurrence of 237 LPM cases during follow-up we had limited statistical power. And even though the consistently neutral or even negative HRs for LPM, we cannot rule out that a family history of LPM has a marginally detrimental effect on LPM risk in individuals with CD.

In this nationwide study, we used biopsy registers to ascertain cases with CD. An earlier evaluation has shown that VA has a high positive predictive value for CD (95%),[21] and that biopsy registers have a high sensitivity for diagnosed CD since more than 96% of Swedish paediatricians and gastroenterologists biopsy individuals before CD diagnosis.[21] The median number of tissue pieces obtained at each small intestinal biopsy in our dataset was 3,[41] and this should detect some 95% of all CD.[42] When two independent examiners examined more than 1500 biopsy reports with VA or inflammation, non-CD diagnoses were rare in VA, with IBD being the most common differential diagnosis and mentioned in 0.3% of reports. In a subset of individuals with CD undergoing medical record validation, some 79% had gastrointestinal symptoms and 35% had anaemia at time of CD diagnosis.[21]

At least 99% of all cancers in Sweden are morphologically verified. Through the Swedish Cancer Register we had long follow-up and were able to ascertain cancer in first-degree relatives and spouses back until 1958.[26] More than 96% of all cancers are reported to this register.[27]

In conclusion, we found no evidence that a family history of LPM or any cancer increases the risk of future LPM in individuals with CD. Despite the large number of study participants, this study was however limited by few positive events due to a low absolute risk of LPM even in individuals with CD, and future studies need larger datasets, but also to consider dietary adherence, smoking and other potential LPM risk factors, to fully rule out that an LPM family history may increase the risk of LPM in individuals with CD.

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Competing interest statement

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Abbreviations used in this article

CD	Celiac disease
CI	Confidence Interval
HR	Hazard Ratio
LPM	Lymphoproliferative malignancy
NHL	Non-Hodgkin Lymphoma
OR	odds ratio
VA	Villous atrophy

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APPENDIX

The Swedish histopathology SnoMed classification compared to other international histopathology classifications.

Classification used in this project	Villous atrophy		
Marsh Classification	Type IIIa	Type IIIb	Type IIIc
Marsh Description	Flat destructive		
Corazza <i>et al</i> (A)	Grade B1		Grade B2
SnoMed Codes	M58, D6218, M58005	M58, D6218, M58006	M58, D6218, M58007
KVAST/Alexander classification	III Partial VA	IV Subtotal VA	IV Total VA
Characteristics			

Classification used in this project	Villous atrophy		
Villous atrophy	+	++	++
IEL#	+	+	+
Crypt hyperplasia	+	++	++

Comparison of small intestinal histopathology classifications. REF A.

Corazza GR, Villanacci V, Zambelli C, *et al.* Comparison of the interobserver reproducibility with different histologic criteria used in celiac disease. *Clin Gastroenterol Hepatol.* Jul 2007;5(7):838–843.

Figure 1. Flowchart of study participants

LPM, lymphoproliferative malignancy. Ca, cancer. HR, Hazard ratios.

Thin arrows signify comparisons with matched general population controls. Thick arrows show internal comparisons. Values given in the separate boxed at the bottom of the figure are hazard ratios (HRs) for LPM.

For instance:

Thin arrow: CD patients with a family history of LPM (n=616) were at a 1.18-fold increased risk of later LPM compared to general population controls.

Thick arrow: CD patients with family history of LPM (n=616) were at lower risk of LPM (HR=0.31) than CD patients without a family history of LPM (n=28,380).

Table 1

Characteristics of study participants with Celiac Disease

Celiac disease	Family history of LPM		Family history of any Cancer	
	Yes	No	Yes	No
Total	616	28,380	8,439*	20,557*
Females (%)	367 (59.6)	17,594 (62.0)	5,228 (62.0)	12,733 (61.9)
Males (%)	249 (40.4)	10,786 (38.0)	3,211 (38.0)	7,824 (38.1)
<i>Age (years)#</i>				
0–19 (%)	67 (10.9)	11,730 (41.3)	1,481 (17.5)	10,316 (50.2)
20–39 (%)	167 (27.1)	5,144 (18.1)	2,031 (24.1)	3,280 (16.0)
40–59 (%)	288 (46.8)	6,161 (21.7)	3,487 (41.3)	2,962 (14.4)
60 (%)	94 (15.3)	5,345 (18.8)	1,440 (17.1)	3,999 (19.5)
<i>Calendar year#</i>				
–1989	114 (18.5)	3,979 (14.0)	1,233 (14.6)	2,860 (13.9)
1990–99	252 (40.9)	11,772 (41.5)	3,482 (41.3)	8,542 (41.6)
2000–	250 (40.6)	12,629 (44.5)	3,724 (44.1)	9,155 (44.5)

* Distribution of sex, age, and calendar year were identical in general population controls since controls were matched for these variables.

At time of celiac disease diagnosis

Table 2

Risk of lymphoproliferative malignancy in individuals with celiac disease according to family history of lymphoproliferative malignancy or any cancer. Comparison with general population controls.

Family history of cancer	N	Obs.*	Exp.*	Hazard ratios; 95%CI	p-values	Person-years	Incidence per 100,000 #
<i>First-degree</i>							
LPM	616	2	2	1.18; 0.27–5.10	0.827	7,605	26
No LPM	28,380	235	82	2.86; 2.44–3.36	<0.001	317,566	74
Any cancer	8,439	60	30	2.00; 1.50–2.68	<0.001	98,541	30
No cancer	20,557	177	54	3.29; 2.73–3.97	<0.001	226,630	78
<i>Spouse</i>							
LPM	41	0	-	-	-	462	-
No LPM	28,955	237	122	2.84; 2.42–3.33	<0.001	324,710	38
Any cancer	856	6	7	0.88; 0.37–2.09	0.779	10,102	59
No cancer	28,140	231	77	3.00; 2.55–3.52	<0.001	315,070	24

LPM, Lymphoproliferative malignancy

Obs, Observed number of LPM in individuals with celiac disease. Exp, Expected.

* Number of LPM in individuals with celiac disease

Number of LPM per 100,000 person-years

Table 3

Risk of lymphoproliferative malignancy in individuals with celiac disease according to family history of any cancer. Subanalyses. Comparison with general population.

	Hazard ratios; 95%CI	
	Family history of any cancer	No family history of any cancer
<i>Sex</i>		
Female	2.48; 1.69–3.62	3.39; 2.59–4.43
Male	1.55; 0.99–2.43	3.21; 2.47–4.17
<i>Age[*] (years)</i>		
0–19 [#]	-	1.14; 0.51–2.56
20–39	0.36; 0.05–2.69	5.72; 2.56–12.75
40–59	2.33; 1.59–3.42	3.79; 2.68–5.36
60	2.25; 1.40–3.62	3.33; 2.61–4.26
<i>Calendar year[*]</i>		
-1989	1.79; 0.28–3.15	4.02; 2.77–5.78
1990–99	1.61; 1.04–2.48	2.74; 2.08–3.60
2000–	2.86; 1.78–4.58	3.87; 2.68–5.58

LPM, Lymphoproliferative malignancy

^{*} At celiac disease diagnosis, and corresponding date in matched controls.

[#] No HR was estimated for individuals diagnosed with CD in childhood and a family history of cancer due to lack of LPM in celiac individuals in this category.

Interpretation of table. E.g. Females with CD and a family history of any cancer were at a 2.48-fold increased risk of developing lymphoproliferative malignancy compared to females in the general population.

Table 4

Risk of lymphoproliferative malignancy in celiac individuals with a family history of cancer vs. celiac individuals without a family history of cancer

Family history	Crude		Adjusted	
	Hazard ratios; 95%CI	p-values	Hazard ratios; 95%CI	p-values
LPM	0.37; 0.09–1.48	0.159	0.31; 0.08–1.23	0.096
Any cancer	0.79; 0.59–1.06	0.118	0.60; 0.44–0.81	0.001

LPM, Lymphoproliferative malignancy

Adjusted for sex, calendar period, and age at CD diagnosis (10-year-increments) Interpretation of table. E.g. Adjusting for sex, calendar period and age, individuals CD who had a family history of any cancer were at a lower risk of developing lymphoproliferative malignancy compared to individuals who had no family history of cancer (HR=0.60). The risk reduction was 40% (1 minus 0.60).