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Lymphoma risk following celiac disease diagnosed in Sweden from the mid-1970s to the early 21st Century

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Abstract

Background—Celiac disease (CD), a common digestive disease, is well-known to be associated with excess non-Hodgkin lymphoma (NHL) risk. However, there are only limited data on risk in the current era of serologic testing and human leukocytes antigen (HLA) typing to screen for CD. Also, there is no information on the role of family history of CD in relation to lymphoma risk.

Methods—We identified 37,869 NHL, 8323 Hodgkin lymphoma (HL), 13,842 chronic lymphocytic leukemia (CLL) patients diagnosed in Sweden 1965–2004, 236,408 matched controls, and 613,961 first-degree relatives. Using logistic regression, we calculated odds ratios (ORs) and 95% confidence intervals (CIs) as measures of risks adjusted for matching factors.

Results—Overall we found persons with a hospital discharge diagnosis of CD to have a 5.35-fold (95% CI=3.56–8.06) increased NHL risk. Risk of HL was borderline increased (OR=2.54, 95% CI=0.99–6.56); however, there was no excess CLL risk. Persons diagnosed with CD in 1975–1984, 1985–1994, and 1995–2004 had a 13.2-fold (95% CI=3.63–48.0), 7.90-fold (95% CI=3.38–18.5), and 3.84-fold (95% CI=2.28–6.45) increased risk of NHL, respectively ($P_{\text{trend}} < 0.0001$). Individuals with a sibling affected with CD had a 2.03-fold (95% CI=1.29–3.19) increased NHL risk.

Conclusions—Persons with CD have an increased NHL risk; however, the excess risk has tapered off substantially in the last four decades. The observed excess NHL risk among individuals with a sibling affected with CD suggests shared susceptibility. Future studies are needed to explore the roles of gluten intake, secondary intestinal inflammation, and susceptibility genes in relation to subsequent risk of developing lymphoma.

Keywords

Celiac disease; secular trend; family history; risk; lymphoma; shared susceptibility

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INTRODUCTION

Celiac disease (CD) is characterized by a T-cell-mediated response to ingested wheat gluten and related proteins of rye and barley. This response leads to a chronic inflammation with autoimmune features typified by diffuse damage to the proximal small intestinal mucosa that results in malabsorption of most nutrients^{1, 2}. The disease has a wide spectrum of clinical manifestations including diarrhea, abdominal distention, abdominal pain, weight loss, fatigue, malnutrition, and osteoporosis^{3, 4}. CD may also present with extra intestinal manifestations such as dermatitis herpetiformis, iron deficiency, and short stature.

The gold standard for CD diagnosis is duodenal biopsy, showing characteristic, though not specific, intraepithelial lymphocytosis, crypt hyperplasia and various degrees of villous height reduction, together with symptomatic and histological improvement on dietary gluten withdrawal. Today, in clinical practice, serologic testing (IgA anti human tissue transglutaminase (TTG) and IgA endomysial antibody immunofluorescence (EMA)) and human leukocytes antigen (HLA) typing (HLA-DQ1 and HLA-DQ8) are commonly used techniques with reported 90% sensitivity and specificity, to screen persons with a clinical suspicion for CD, and to better identify candidates for intestinal biopsy³. As a consequence of these commonly available screening tools, today, CD is considered one of the most common digestive diseases in humans with an estimated prevalence of 1:100 to 1:300 in North America and Europe^{1, 5}. CD is possibly affecting as many as 3 million American, or roughly 1% of the U.S. population. The only effective treatment to date is a gluten-free diet.

For over 70 years, it has been recognized that CD is associated with an increased risk of developing non-Hodgkin lymphoma (NHL)⁶. Risks have been consistently reported to be highest for enteropathy-type T-cell lymphoma (ETL) and B-cell NHL of the gut (odds ratios [ORs] over 10); however, extra intestinal lymphomas including Hodgkin lymphoma (HL) have also been observed^{7, 8}. Earlier studies reported CD to be associated with up to 100-fold elevated risk of lymphoma^{9, 10}. However, more recent investigations, primarily focusing on the mid-1970s to the mid-1990s, have estimated the excess risk of lymphoma among persons with CD to be more modest reflected in ORs ranging from 2 to 11 (Table 1)^{7, 8, 11-25}. At this time, there are only sparse data available on the risk of lymphoma among patients diagnosed with CD using modern and widely available serologic testing and HLA typing. Indeed, to our knowledge, no large epidemiologic study has been carried out to define the association between CD and following lymphoma risk in the early 21st Century, comparing with a group of patients from the same population in earlier years. This is of clinical importance in that it allows us to establish the impact of early detection and treatment of CD in the context of lymphomagenesis.

We have conducted a comprehensive population-based case-control study including over 60,000 lymphoma patients diagnosed in Sweden 1965-2004, almost 240,000 frequency matched controls; and more than 750,000 linkable relatives of patients and controls. Because CD has been found to be associated with excess risk of extra intestinal lymphomas, we expanded our study to include all types of lymphomas (NHL, HL, and chronic lymphocytic leukemia [CLL]). The aim of our study was to quantify secular trend of lymphoma risks among individuals with a prior diagnosis of CD. In particular, we were interested in assessing the relationship between CD and lymphoma during the past decade (1995-2004), in the era of commonly available serologic markers and HLA typing screening tools^{5, 26, 27}. Furthermore, CD shows inherited predisposition where first-degree relatives have a 5-10% risk of CD (depending on the screening method), the highest risk being found in siblings at risk with the HLA genotypes²⁸. One could hypothesize that the association of lymphoma and CD is due to common genes predisposing to both conditions. This would predict

aggregation of CD and lymphoma in the same families. To test this hypothesis, we tested for increased risk of lymphoma among individuals with a family history of CD.

METHODS

Central registries, patients, controls and first-degree relatives

All residents of Sweden are, upon birth or immigration, assigned a unique national registration number that is used in government maintained nationwide healthcare and population registers, whereby record linkage is possible with a high degree of accuracy. For each individual the date of death is centrally registered in the Swedish Cause of Death Registry.

Since 1958, all physicians and pathologists/cytologists in Sweden are obliged by law to report each incident case of cancer which they diagnose and/or treat, to the centralized nationwide Swedish Cancer Registry. The Registry contains information on diagnosis, sex, date of birth, date of diagnosis, and region/hospital where the diagnosis was made²⁹. In a recent validation study focusing on lymphoproliferative hematologic tumors diagnosed 1964-2003, we found the completeness and the diagnostic accuracy of the Registry to be >90-95%³⁰.

In this study, we identified all living incident patients diagnosed from January 1, 1965 to December 30, 2004 with NHL, HL, and CLL from the nationwide Swedish Cancer Registry. For each lymphoma patient, four population-based controls matched by sex, year of birth, and county of residence were chosen randomly from the Swedish Population database. All controls had to be alive at the time of lymphoma diagnosis (index date) for the corresponding case and free of cancer at the index date.

From the Swedish Multigenerational Registry³¹, which includes information on parent-offspring relations for all Swedish citizens who were born 1932 and later, we obtained information on all linkable first-degree relatives (parents, siblings, and offspring) for cases and controls, and linked them to the Swedish Cancer Registry in order to obtain information on living incident cancer cases.

All patients, controls, and relatives were further linked with the Swedish Inpatient Registry 1964-2005³¹, which contains information on discharge diagnoses and discharge listing from inpatient care (coded according to ICD-7 to ICD-10), which had a gradually increasing geographical coverage (50% of the population in the mid-1970s and by 1987 all counties were included)^{31, 32}. Through this linkage, we collected information on patients who were diagnosed as CD.

Approval was obtained from the Karolinska Institutional Review Board (IRB) for this study. Informed consent was waived because we had no contact with study subjects. An exemption from IRB review was obtained from the NIH Office of Human Subjects Research because we used existing data without personal identifiers.

Statistical analysis

To avoid inclusion of lymphoma patients with CD as a presenting feature, to reduce potential surveillance bias, and to prevent counting CD that was recorded only among patients as secondary diagnoses at admissions for symptoms of lymphoma, we did not capture information on CD up to one year prior to lymphoma diagnosis (for controls, one year prior to the index date).

First, we calculated overall ORs with 95% confidence intervals (CIs) as measures of association between lymphoma risk and personal history of CD using unconditional logistic regression, adjusting for the matching factors: gender, year of birth, calendar period of lymphoma diagnosis for cases and index date for controls, and county. To validate this model, we also conducted analyses using conditional logistic regression according to the matched design. Given the models resulted in similar results, we only present results from unconditional logistic regression. Second, to explore if there were interactions with age and gender we conducted stratifying analyses by gender and age. In accord with prior studies, we used the following cut-off for age: NHL and CLL ^{33, 34} (above/below 65 years) and HL ³⁵ (above/below 45 years). Third, we analyzed the association between CD and lymphoma by latency (i.e. the time between the first discharge record diagnosis of CD and the date of lymphoma diagnosis for cases or index date for controls: 1-4.99 years, 5-9.99 years, and 10 or more years). Fourth, we evaluated the association by calendar period of lymphoma diagnosis for cases and index date for controls (1965-1974, 1975-1984, 1985-1994, and 1995-2004). Lastly, we quantified the risk of developing lymphoma among persons with a parent, sibling or offspring affected with CD (i.e., family history of CD). Using logistic regression models (adjusted for gender, year of birth, calendar period of lymphoma diagnosis or index date, county, and personal history of CD), we calculated ORs as measures of relative risks. In sub-analyses, we defined relative risks stratifying by gender and age.

RESULTS

As shown in Table 2, we included 37,869 NHL, 8,323 HL, and 13,842 CLL patients; 236,408 frequency matched controls; and 753,983 linkable first-degree relatives of patients and controls. About 60% of the lymphoma patients were males. Median age at diagnosis was 69 years, 52 years, and 72 years, for NHL, HL, and CLL patients, respectively.

Personal history of CD and risk of NHL

After excluding individuals with a diagnosis of lymphoma within one year after CD diagnosis, there were a total of 54 NHL patients and 40 frequency matched controls with a personal history of CD. As shown in Table 3, an overall 5-fold increased risk for developing NHL (OR=5.35, 95% CI=3.56-8.06) was estimated. In stratified analyses, we found the risk of NHL to be higher for females (OR=7.12, 95% CI=3.87-13.1) than males (OR=4.16, 95% CI=2.38-7.29); however, the difference was not significant ($P_{\text{interaction}}=0.20$). Although the association between CD and NHL was more prominent among persons diagnosed with NHL before the age of 65 years (OR=6.71, 95% CI=3.54-12.7) compared to those diagnosed at the age of 65 years or older (OR=4.55, 95% CI=2.66-7.77), the difference was not significant ($P_{\text{interaction}}=0.50$).

When we assessed NHL risk in relation to the time between a first hospitalization for CD and a subsequent NHL diagnosis (i.e. latency) (Table 3), we found risk of NHL to be most prominent in the first latency period (1-5 years) (OR=7.64, 95% CI=4.18-14.0). Although NHL risk declined with latency elongation ($p_{\text{trend}} < 0.0001$), the risk was still highly elevated after 10 years latency (OR=3.98, 95% CI=1.72-9.17).

When the association was evaluated by calendar year period, we found persons diagnosed with CD in 1975-1984, 1985-1994, and 1995-2004 to have 13.2-fold (95% CI=3.63-48.0), 7.90-fold (95% CI=3.38-18.5), and 3.84-fold (95% CI=2.28-6.45) risk of developing NHL respectively ($P_{\text{trend}} < 0.0001$) (Table 3) (Figure 1). In our database, there were no individuals diagnosed with CD between 1965 and 1974.

Family history of CD and risk of NHL

We observed a total of 76 NHL patients and 271 controls with a family member (parents, sibling or offspring) affected with CD. When adjusting for personal history of CD, we found no overall increased risk of NHL (OR= 1.12, 95% CI=0.87-1.45) among persons with a first-degree relative affected with CD (Table 3). However, when we assessed NHL risk by type of first-degree relative, we found a 2-fold (OR=2.03, 95% CI=1.29-3.19) excess risk among persons with a sibling affected with CD. In contrast, we found no statistical association between NHL risk and having a parent or an offspring diagnosed with CD.

Personal and family history of CD and risk of HL and CLL

Based on 7 HL and 4 CLL patients with a personal history of CD, we found a borderline significant association between a personal history of CD and the subsequent risk of developing HL (OR=2.54, 95% CI=0.99-6.56). However, for CLL there was no significant excess risk (OR=1.12, 95% CI=0.37-3.41). When we assessed the risk by gender, males affected with CD had a borderline elevated risk of HL (OR=3.32, 95% CI=1.01-10.9), but the risk was not different between males and females ($P_{\text{interaction}}=0.48$). Among individuals diagnosed with HL at age 45 years or older, we found CD to be associated with 4-fold risk increase (OR=3.97, 95% CI=1.28-12.3). Again, the difference in risk between different age groups was not significant ($P_{\text{interaction}}=0.83$). Among HL and CLL patients, we observed a total of 14 and 11 patients, respectively, to have a relative affected with CD. Overall we found no statistical association between a family history of CD and risk of developing HL or CLL.

DISCUSSION

In this large population-based study based on Swedish high quality data obtained over four decades, we found individuals with a hospital discharge diagnosis of CD to have an overall 5.4-fold increased risk of developing NHL. However, there was no significantly increased risk of HL or CLL. When we defined risk of NHL by calendar period, it exhibited a steady decline: a highly elevated 13.2-fold risk in the earlier years (1975-1984), a 7.9-fold increased risk in the following decade (1985-1994), and a more moderately 3.8-fold increased risk in the most recent decade (1995-2004). These findings have clinical implications for patients and health care professional in that they shed light on the impact of modern serologic markers and HLA typing for CD diagnosis in clinical practice, as well as early treatment (i.e. gluten-free diet), to reduce the risk of developing NHL. While diagnosis is more accurate and specific, it is more likely that milder cases are increasingly detected. Clinic presentation of diarrhea and mal-absorption are less common and atypical and silent presentations are increasing. Furthermore, for the first time, in this investigation we found a significantly increased risk of NHL among individual with a sibling affected by CD. This finding supports the operation of shared (genetic or environmental, or both) susceptibility for NHL and CD and it needs to be followed-up in future investigations.

Our findings confirm and expand on the results from a prior survey by Askling et al. who assessed lymphoma risk among a cohort of patients with a hospital discharge diagnosis of CD between 1964 and 1995⁷. In their study, a decreased trend of standardized incidence ratios (SIRs) for overall lymphomas (including NHL and HL patients combined) was observed. In our investigation (including 37,869 NHL, 8323 HL, 13,842 CLL patients diagnosed in Sweden 1965-2004 and 236,408 matched controls), we were able to quantify risks over time for NHL, HL, and CLL separately. A novel and important clinical message from our study, is the finding that persons diagnosed with CD in present time have a substantially lower risk of developing NHL than previously published studies based on CD diagnosed in earlier years^{7, 10, 16, 21}. We also observed 7 HL cases with a prior diagnosis of

CD (OR=2.54, 95% CI=0.99-6.56). Based on only 4 cases, we found no excess risk of CLL following CD.

Our study is unique in that it provides population-based information on lymphoma risk based on a large number of patients diagnosed with CD in the era of modern serologic markers and HLA typing. Simultaneously, for comparison over time, our study also gives the risk of lymphoma among a large group of patients diagnosed with CD in earlier years in the same population. There are several explanations for the decreased risk of NHL over time.

Primarily, serologic markers and HLA typing for CD have been developed to non-invasively screen persons with symptoms suspicious for CD, and to allow identification of persons who might be candidates for duodenal biopsy, the gold standard method to diagnose CD³. The increased use of serologic markers and HLA typing has contributed to increased detection rate of early stage (atypical or silent) CD^{26,27}. Based on our clinical experience, in Sweden, serologic markers and HLA typing have been widely used in clinical practice since the mid 1990s. Current estimations indicate that the prevalence of CD in North America and Europe, as well as Asia, is about 1:100 to 1:300^{1,5,36}, but is thought to be under-diagnosed. Although the literature is not consistent³⁷⁻⁴⁰, a gluten-free diet is highly effective in eliminating CD-characteristic intestinal lesions. Prior studies have shown that gluten-free diet induces clinical improvement and histological recovery^{41,42}. In Sweden, since the late 1970s, federal laws [SFS 1979:1132] state that public preschools are required to provide a gluten-free diet to children with CD⁴³. On a national level, the awareness of gluten-free diet for persons affected with CD has been increasing since then. Consequently, it is reasonable to hypothesize that lymphomagenesis among CD patients is due to secondary intestinal inflammation. Based on these facts, one explanation might be that early detection of CD in recent years has allowed the responsible clinician to provide dietary guidance to the patients, and thereby prevent complications including lymphoma development. Another explanation might be that the detection of CD in individuals who are asymptomatic or in an earlier stage (i.e. less severe intestinal inflammation and immune disruption at diagnosis) results in a lower risk of developing lymphoma per se. Alternatively there might be a combination of these mechanisms, or other factors might be involved as well. Also, many cases may have manifested various symptoms including intestinal atrophy that in some cases were due to other disorders (such as other autoimmune diseases) that were strongly associated with NHL. More specific diagnostic tools have enabled better diagnostic accuracy, eliminating these cases. Independent of the exact underlying mechanisms, our findings are important in that they provide novel clinical insights of value for both patients and health care professionals. Future prospective studies monitoring gluten intake, intestinal inflammation, and risks of developing lymphomas are needed to better understand the operation of these capacities.

Our finding of an increased lymphoma risk among persons with a sibling affected with CD suggests that there might be some common genes causing risk to both CD and lymphoma. CD has been shown to have a significant heritable component, partly due to HLA DQ2 or DQ8 genotypes⁴⁴. However, HLA does not account for all of the familial aggregation and there is some evidence for the involvement of other non-HLA genes^{44,45}. The fact that CD aggregates most strongly in siblings²⁸ suggests recessive inheritance or gene dosage effects. Our observation that there was a familial association between lymphoma and CD only in siblings suggests a similar mechanism that could involve the HLA region, or other immune/inflammatory genes.

Our study is the largest and most comprehensive to date to assess the association of personal history and family history of CD with risk of lymphomas. The population-based approach

involving lymphoma patients, controls, and relatives reduces the possibility for selection bias and eliminates recall-bias. Furthermore, to limit the influence of detection bias, in our risk estimations we excluded lymphomas diagnosed within one year of latency following CD diagnosis. Limitations of our study include incomplete numbers of first-degree relatives of lymphoma patients and controls, lack of information on potential confounders, information on lymphoma subtypes, as well as diagnostic validation and clinical details for single individuals in the study. However, in a previous Swedish study (1964-1994), the validation of hospital registry-based discharge diagnoses for CD was found to be very high ⁷. Another limitation is the lack of outpatient data since which would be expected to lead to under-ascertainment of CD. However, since personal and family history of CD were assessed among matched controls using the same hospital discharge registries, under-diagnosis of CD in subjects or their first-degree relatives should be non-differential between lymphoma patients and their matched controls, and thus any bias should have been conservative. Finally, as pointed out previously ⁴⁶, a potential consideration with the use of a hospital-based register is the fact that persons affected with CD may have a more severe type of disease. However, in Sweden, particularly in earlier years, hospital admissions were common for gastrointestinal work-up and even today some individuals are admitted to hospital when undergoing endoscopy with general anesthesia. Overall, our CD cohort contains both patients hospitalized for either diagnostic or therapeutic reasons, as well as those hospitalized for other medical conditions. Therefore, our results may not be applicable to individuals with asymptomatic CD diagnosed through screening.

In summary, during the entire study-period, we found individuals with CD to have an overall 5.4-fold increased risk of developing NHL, but no statistically increased risk of developing HL or CLL. When we estimated risks of developing NHL among patients diagnosed with CD in the recent decade, compared to those diagnosed with CD in 1975-1984 in the same population, we observed the risk to drop from over 30-fold to 3.8-fold excess. Our observation that NHL risk was increased among persons with a sibling affected with CD suggests shared susceptibility for CD and NHL. There is great need to improve our understanding regarding underlying mechanisms of our findings and to develop better biomarkers for prediction of lymphomagenesis among patients with immune-related and inflammatory conditions ^{34, 35}.

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REFERENCES

1. Ciclitira PJ, Johnson MW, Dewar DH, Ellis HJ. The pathogenesis of coeliac disease. *Mol Aspects Med.* Dec; 2005 26(6):421–458. [PubMed: 16125764]
2. Green PH, Cellier C. Celiac disease. *N Engl J Med.* Oct 25; 2007 357(17):1731–1743. [PubMed: 17960014]
3. Green PH, Rostami K, Marsh MN. Diagnosis of coeliac disease. *Best Pract Res Clin Gastroenterol.* Jun; 2005 19(3):389–400. [PubMed: 15925844]
4. Fasano A. Clinical presentation of celiac disease in the pediatric population. *Gastroenterology.* Apr; 2005 128(4 Suppl 1):S68–73. [PubMed: 15825129]
5. Fasano A, Berti I, Gerarduzzi T, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. *Arch Intern Med.* Feb 10; 2003 163(3):286–292. [PubMed: 12578508]

6. Fairly NHMF. The clinical and biochemical syndrome in lymphoma and allied diseases involving the mesenteric lymph glands. *BMJ*. 1937; 1:375–380. [PubMed: 20780486]
7. Askling J, Linet M, Gridley G, Halstensen TS, Ekstrom K, Ekbom A. Cancer incidence in a population-based cohort of individuals hospitalized with celiac disease or dermatitis herpetiformis. *Gastroenterology*. Nov; 2002 123(5):1428–1435. [PubMed: 12404215]
8. Goldacre MJ, Wotton CJ, Yeates D, Seagroatt V, Jewell D. Cancer in patients with ulcerative colitis, Crohn's disease and coeliac disease: record linkage study. *Eur J Gastroenterol Hepatol*. Apr; 2008 20(4):297–304. [PubMed: 18334873]
9. Fasano A, Catassi C. Current approaches to diagnosis and treatment of celiac disease: an evolving spectrum. *Gastroenterology*. Feb; 2001 120(3):636–651. [PubMed: 11179241]
10. Leonard JN, Tucker WF, Fry JS, et al. Increased incidence of malignancy in dermatitis herpetiformis. *Br Med J (Clin Res Ed)*. Jan 1; 1983 286(6358):16–18.
11. Anderson LA, McMillan SA, Watson RG, et al. Malignancy and mortality in a population-based cohort of patients with coeliac disease or “gluten sensitivity”. *World J Gastroenterol*. Jan 7; 2007 13(1):146–151. [PubMed: 17206762]
12. Silano M, Volta U, Mecchia AM, Dessi M, Di Benedetto R, De Vincenzi M. Delayed diagnosis of coeliac disease increases cancer risk. *BMC Gastroenterol*. 2007; 7:8. [PubMed: 17349035]
13. Smedby KE, Hjalgrim H, Askling J, et al. Autoimmune and chronic inflammatory disorders and risk of non-Hodgkin lymphoma by subtype. *J Natl Cancer Inst*. Jan 4; 2006 98(1):51–60. [PubMed: 16391371]
14. Mearin ML, Catassi C, Brousse N, et al. European multi-centre study on coeliac disease and non-Hodgkin lymphoma. *Eur J Gastroenterol Hepatol*. Feb; 2006 18(2):187–194. [PubMed: 16394801]
15. Viljamaa M, Kaukinen K, Pukkala E, Hervonen K, Reunala T, Collin P. Malignancies and mortality in patients with coeliac disease and dermatitis herpetiformis: 30-year population-based study. *Dig Liver Dis*. Jun; 2006 38(6):374–380. [PubMed: 16627018]
16. Smedby KE, Akerman M, Hildebrand H, Glimelius B, Ekbom A, Askling J. Malignant lymphomas in coeliac disease: evidence of increased risks for lymphoma types other than enteropathy-type T cell lymphoma. *Gut*. Jan; 2005 54(1):54–59. [PubMed: 15591504]
17. Card TR, West J, Holmes GK. Risk of malignancy in diagnosed coeliac disease: a 24-year prospective, population-based, cohort study. *Aliment Pharmacol Ther*. Oct 1; 2004 20(7):769–775. [PubMed: 15379837]
18. West J, Logan RF, Smith CJ, Hubbard RB, Card TR. Malignancy and mortality in people with coeliac disease: population based cohort study. *Bmj*. Sep 25; 2004 329(7468):716–719. [PubMed: 15269095]
19. Farre C, Domingo-Domenech E, Font R, et al. Celiac disease and lymphoma risk: a multicentric case-control study in Spain. *Dig Dis Sci*. Mar; 2004 49(3):408–412. [PubMed: 15139489]
20. Green PH, Fleischauer AT, Bhagat G, Goyal R, Jabri B, Neugut AI. Risk of malignancy in patients with celiac disease. *Am J Med*. Aug 15; 2003 115(3):191–195. [PubMed: 12935825]
21. Peters U, Askling J, Gridley G, Ekbom A, Linet M. Causes of death in patients with celiac disease in a population-based Swedish cohort. *Arch Intern Med*. Jul 14; 2003 163(13):1566–1572. [PubMed: 12860579]
22. Howdle PD, Jalal PK, Holmes GK, Houlston RS. Primary small-bowel malignancy in the UK and its association with coeliac disease. *Qjm*. May; 2003 96(5):345–353. [PubMed: 12702783]
23. Catassi C, Fabiani E, Corrao G, et al. Risk of non-Hodgkin lymphoma in celiac disease. *Jama*. Mar 20; 2002 287(11):1413–1419. [PubMed: 11903028]
24. Green PHR, Stavropoulos SN, Panagi SG, et al. Characteristics of adult celiac disease in the USA: results of a national survey. *Am J Gastroenterol*. Jan; 2001 96(1):126–131. [PubMed: 11197241]
25. Cottone M, Termini A, Oliva L, et al. Mortality and causes of death in celiac disease in a Mediterranean area. *Dig Dis Sci*. Dec; 1999 44(12):2538–2541. [PubMed: 10630509]
26. Catassi C, Fabiani E, Ratsch IM, et al. The coeliac iceberg in Italy. A multicentre antigliadin antibodies screening for coeliac disease in school-age subjects. *Acta Paediatr Suppl*. May.1996 412:29–35. [PubMed: 8783752]

27. Bonamico M, Ferri M, Mariani P, et al. Serologic and genetic markers of celiac disease: a sequential study in the screening of first degree relatives. *J Pediatr Gastroenterol Nutr.* Feb; 2006 42(2):150–154. [PubMed: 16456406]
28. Rubio-Tapia A, Van Dyke CT, Lahr BD, et al. Predictors of Family Risk for Celiac Disease: A Population-Based Study. *Clin Gastroenterol Hepatol.* Jun 26.2008
29. Socialstyrelsen. Cancer incidence in Sweden 2001. 2003.
30. Turesson I, Linet MS, Bjorkholm M, et al. Ascertainment and diagnostic accuracy for hematopoietic lymphoproliferative malignancies in Sweden 1964–2003. *Int J Cancer.* Jun 21.2007
31. Skarle, A. Stockholm (Sweden): Statistics Sweden, Population Statistics. 2001.
32. The National Board of Health and Welfare. Cancer Incidence in Sweden 2003. Stockholm: 2004.
33. Landgren O, Engels EA, Caporaso NE, et al. Patterns of autoimmunity and subsequent chronic lymphocytic leukemia in Nordic countries. *Blood.* Jul 1; 2006 108(1):292–296. [PubMed: 16527887]
34. Mellemkjaer L, Pfeiffer RM, Engels EA, et al. Autoimmune disease in individuals and close family members and susceptibility to non-Hodgkin's lymphoma. *Arthritis Rheum.* Mar; 2008 58(3):657–666. [PubMed: 18311836]
35. Landgren O, Engels EA, Pfeiffer RM, et al. Autoimmunity and susceptibility to Hodgkin lymphoma: a population-based case-control study in Scandinavia. *J Natl Cancer Inst.* Sep 20; 2006 98(18):1321–1330. [PubMed: 16985251]
36. National Institutes of Health Consensus Development Conference Statement on Celiac Disease, June 28–30, 2004. *Gastroenterology.* Apr; 2005 128(4 Suppl 1):S1–9. [PubMed: 15825115]
37. Hall RP. Dietary management of dermatitis herpetiformis. *Arch Dermatol.* Oct; 1987 123(10): 1378a–1380a.
38. Janatuinen EK, Kemppainen TA, Julkunen RJ, et al. No harm from five year ingestion of oats in coeliac disease. *Gut.* Mar; 2002 50(3):332–335. [PubMed: 11839710]
39. Kumar PJ, Farthing MG. Oats and celiac disease. *N Engl J Med.* Oct 19; 1995 333(16):1075–1076. [PubMed: 7675053]
40. Hogberg L, Grodzinsky E, Stenhammar L. Better dietary compliance in patients with coeliac disease diagnosed in early childhood. *Scand J Gastroenterol.* Jul; 2003 38(7):751–754. [PubMed: 12889562]
41. Lee SK, Lo W, Memeo L, Rotterdam H, Green PH. Duodenal histology in patients with celiac disease after treatment with a gluten-free diet. *Gastrointest Endosc.* Feb; 2003 57(2):187–191. [PubMed: 12556782]
42. Matysiak-Budnik T, Malamut G, de Serre NP, et al. Long-term follow-up of 61 coeliac patients diagnosed in childhood: evolution toward latency is possible on a normal diet. *Gut.* Oct; 2007 56(10):1379–1386. [PubMed: 17303598]
43. Mikkelsen A, Borres M, Kristiansson B, Odenman I. Different policy on gluten-free food in child day care centers. Unified national guidelines are needed. *Lakartidningen.* Apr 15; 1998 95(16): 1820–1822. 1824. [PubMed: 9599489]
44. Louka AS, Sollid LM. HLA in coeliac disease: unravelling the complex genetics of a complex disorder. *Tissue Antigens.* Feb; 2003 61(2):105–117. [PubMed: 12694579]
45. Monsuur AJ, Wijmenga C. Understanding the molecular basis of celiac disease: what genetic studies reveal. *Ann Med.* 2006; 38(8):578–591. [PubMed: 17438672]
46. Olen O, Montgomery SM, Elinder G, Ekblom A, Ludvigsson JF. Increased risk of immune thrombocytopenic purpura among inpatients with coeliac disease. *Scand J Gastroenterol.* 2008; 43(4):416–422. [PubMed: 18365906]

Celiac disease and risk of NHL by calendar period

Figure 1.
CD and risk of NHL by calendar period

Table 1

CD and risk of lymphomas in selected reported studies

Location	Lymphoma cases, n	CD cases, n	Personal history of CD and lymphoma risk	Study design	Study period	Reference
United Kingdom	11	1997	RR=3.28 * NHL RR=5.07 HL	Hospital-based cohort	1963-1999	Goldacre et al 2008 ⁸
United Kingdom	2	490	SIR=7.47 * NHL	Population-based cohort	1993-1996	Anderson et al 2007 ¹¹
Italy	20	1968	SIR=4.7 * NHL	Population-based cohort	1982-2005	Silano et al 2007 ¹²
Denmark and Sweden	3055	28	OR=2.1 * NHL	Population-based case-control	Denmark 2000-2002 Sweden 1999-2002	Snedby et al 2006 ¹³
10 European countries	1446	66	OR=2.6 * NHL	Prospective, multi-center case-control	1998-2001	Mearin et al 2006 ¹⁴
Finland			SIR=3.2 * NHL	Population-based cohort	1960-2000	Viljamaa et al 2006 ¹⁵
Sweden	56	11650	SIR=6.6 * NHL SIR=1.0 HL	Population-based cohort	1970-1995	Smedy et al 2005 ¹⁶
United Kingdom	12	869	SIR=5.8 * NHL	Population-based cohort	1978-2001	Card et al 2004 ¹⁷
United Kingdom	23	4732	HR=4.8 * lymphoma	Population-based cohort	1987-2002	West et al 2004 ¹⁸
Spain	298	5	OR=0.62 lymphoma	Multi-center case-control	1998-2000	Farre et al 2004 ¹⁹
USA	9	381	SMR=5.3-9.1 * NHL	Hospital-based cohort	1981-2000	Green et al 2003 ²⁰
Sweden	22	10032	SMR=11.4 * NHL	Population-based cohort	1964-1993	Peters et al 2003 ²¹
United Kingdom	86	37	37/86 lymphoma	Clinical registry-based cohort	1998-2000	Howdle et al 2003 ²²
Italy	653	6	OR=3.1 * NHL	Multi-center case-control	1996-1999	Catassi et al 2002 ²³
Sweden	11019	44	SIR=6.3 * NHL SIR=4.6 HL	Population-based cohort	1964-1994	Askling et al 2002 ⁷
USA	3	1612	RR=300 lymphoma	Nationwide cross-sectional survey	1996-1997	Green et al 2001 ²⁴
Italy	6	228	6/228 lymphoma	Hospital-based cohort	1980-1997	Cottone et al 1999 ²⁵

Abbreviations: NHL = Non-Hodgkin lymphoma; HL = Hodgkin lymphoma; CLL = chronic lymphocyte leukemia; OR = odds ratio; HR = hazard ratio; RR = relative risk; SIR = standardized incidence ratio; SMR = standardized mortality ratio

* P<0.05

Table 2

Characteristics of lymphoma patients and controls

Variable	NHL		HL		CLL	
	Patients	Controls	Patients	Controls	Patients	Controls
Total number	37869	149740	8323	33160	13824	54508
Age*	69(58-77)		52(29-70)	52(29-69.5)	72(64-79)	72(64-78)
Age group* (%)						
<15y	647(2)	2591(2)	272(3)	1088(3)	6(<1)	24(<1)
15-24y	457(1)	1836(1)	1230(15)	4919(15)	9(<1)	36(0<1)
25-34y	806(2)	3308(2)	1183(14)	4753(14)	44(<1)	175(<1)
35-44y	1730(5)	7102(5)	880(11)	3540(11)	195(1)	779(1)
45-54y	3920(10)	15782(10)	821(10)	3287(10)	949(7)	3792(7)
55-64y	6939(18)	27660(18)	1117(13)	4449(13)	2507(18)	9981(18)
65-74y	10685(28)	42081(28)	1482(18)	5859(18)	4555(33)	17941(33)
>75y	12684(33)	49380(33)	1338(16)	5265(16)	5559(40)	21780(40)
Gender (%)						
Male	20902(55)	83107(55)	4801(58)	19181(58)	8536(62)	33760(62)
Female	16967(45)	66633(45)	3522(42)	13979(42)	5288(38)	20748(38)
Calendar year [#]	1991 (1984-1998)		1982 (1973-1993)		1987 (1978-1997)	
Linkable first-degree relatives, n/N	96186	391109	24362	107556	27074	107696
Parents	17041(0.4)	71345(0.5)	6710(0.8)	28689(0.9)	3215(0.2)	13022(0.2)
Sibling	17877(0.5)	73374(0.5)	6942(0.8)	30448(0.9)	3177(0.2)	12946(0.2)
Offspring	61268(1.6)	246390(1.6)	10710(1.3)	48419(1.5)	20682(1.5)	81728(1.5)

* Age at lymphoma diagnosis (index date for controls), median (interquartile range)

** n/N = number of first-degree relatives per proband

[#] Calendar year at lymphoma diagnosis (index date for controls), median (interquartile range)

Table 3

Personal and family history of CD and risk of NHL

Variable	Patients (n=37,869)	Controls (n=149,740)	OR (95% CI)
Personal history of CD			
Personal history of CD *	54	40	5.35(3.56-8.06)
Gender			
Male	25	24	4.16(2.38-7.29)
Female	29	16	7.12(3.87-13.1)
Age [#] of proband, years			
Younger than 65	25	15	6.70(3.53-12.7)
65 or older	29	25	4.55(2.66-7.77)
Latency ^{**} , years			
1-4.99	31	16	7.64(4.18-14.0)
5-9.99	12	13	3.66(1.67-8.02)
10 or more	11	11	3.98(1.72-9.17)
P _{trend}			<0.0001
Calendar year ^{##}			
1965-1974	0	0	N.A.
1975-1984	10	3	13.2(3.63-48.0)
1985-1994	16	8	7.90(3.38-18.5)
1995-2004	28	29	3.84(2.28-6.45)
P _{trend}			<0.0001
Family history of CD			
Family history of CD	76	271	1.12(0.87-1.45)
Gender of proband			
Male	42	161	1.04(0.75-1.47)
Female	34	110	1.23(0.84-1.81)
Age of proband [#] , years			
Young age (<65)	50	188	1.08(0.79-1.47)
Late age (≥65)	26	83	1.23(0.79-1.91)
Type of first-degree relative			
Parent	9	46	0.79(0.39-1.62)
Mother	4	24	0.67(0.23-1.94)
Father	5	22	0.92(0.35-2.42)
Sibling	28	56	2.03(1.29-3.19)
Offspring	40	170	0.94(0.66-1.32)

Abbreviations:

OR=odds ratio; CI=confidence interval; N.A.=not applicable.

*** Defined as having either a parent, sibling or an offspring affected with CD All logistic regression models were adjusted for birth year, sex, calendar period of lymphoma diagnosis, and region; models estimating risk associated with a family history of CD were also adjusted for personal history of CD.

* Individuals diagnosed with lymphoma (index date for controls) within one year after CD diagnosis were excluded.

** Time between a discharge record diagnosis of CD and a subsequent diagnosis of NHL (index date for controls).

Age at lymphoma diagnosis (index date for controls)

Calendar year at lymphoma diagnosis (index date for controls)