Autoimmune Disease in First-Degree Relatives and Spouses of Individuals With Celiac Disease

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Q8 **BACKGROUND & AIMS:** **First-degree relatives of individuals with celiac disease are at increased risk for this disorder, but little is known about their risk for other autoimmune diseases. We assessed the risk of nonceliac autoimmune disease in first-degree relatives and spouses of people with celiac disease.**

METHODS: **We identified individuals with celiac disease by searching computerized duodenal and jejunal biopsies, collected from 1969 through 2008, at 28 pathology departments in Sweden. Celiac disease was identified based on biopsy reports of villous atrophy (equal to Marsh grade 3; n = 29,096). Individuals with celiac disease were matched with up to 5 controls (people without celiac disease) for sex, age, county, and calendar year (total, 144,522 controls). Through Swedish health care registries, we identified all first-degree relatives (fathers, mothers, siblings, and offspring) and spouses of individuals with celiac disease (n = 84,648) and controls (n = 430,942). We used Cox regression analysis to calculate hazard ratios (HRs) for nonceliac autoimmune disease (Crohn's disease, type 1 diabetes mellitus, hypothyroidism, hyperthyroidism, psoriasis, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus, or ulcerative colitis) in these groups.**

RESULTS: **During the follow-up period (median, 10.8 y), 3333 of the first-degree relatives of patients with celiac disease (3.9%) and 12,860 relatives of controls (3.0%) had an autoimmune disease other than celiac disease. First-degree relatives of people with celiac disease were at increased risk of nonceliac autoimmune disease, compared with controls (HR, 1.28; 95% confidence interval, 1.23–1.33), as were spouses (HR, 1.20; 95% confidence interval, 1.06–1.35). Risk estimates for nonceliac autoimmune disease did not differ between first-degree relatives and spouses of individuals with celiac disease (interaction test: $P = .11$). HRs for celiac disease were highest in the first 2 years of follow-up evaluation.**

CONCLUSIONS: **First-degree relatives and spouses of individuals with celiac disease are at increased risk of nonceliac autoimmune disease. In addition to genetic factors, environmental factors and ascertainment bias might contribute to the increased risk of autoimmunity in first-degree relatives of individuals with celiac disease.**

Q9 *Keywords:* Population Study; Risk Factor; Genetics; Heredity; Celiac; Cohort; Shared Genetics; Autoimmune.

Q10 Q11 Q12 Celiac disease (CD) is characterized by an immune-mediated response to the intake of gluten, resulting in small intestinal villous atrophy.[1] CD affects approximately 1% of the Western population.[2] Earlier data suggested a concordance rate in monozygotic twins of approximately 75%, and development of CD is conditional on genetic background.[3] CD also has been associated with several autoimmune diseases. Therefore, screening for CD is recommended in individuals with certain diseases, such as type I diabetes mellitus (T1DM) and autoimmune thyroid disease.[4] In our recent meta-analysis, approximately 6% of individuals with T1DM had CD, suggesting a more than 5-fold increased relative risk of CD in individuals with T1DM.[5] The

Abbreviations used in this paper: CD, celiac disease; CI, confidence interval; FDR, first-degree relative; HR, hazard ratio; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; T1DM, type I diabetes mellitus; UC, ulcerative colitis.

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association of CD and T1DM is explained partly by shared HLA genetics,[6] and more than 60% of CD-associated loci outside the HLA region identified by genome-wide association studies are shared with at least one other autoimmune disease.[7] Loci within the HLA region also are shared with thyroid autoimmunity and systemic lupus erythematosus (SLE) and the risk loci outside of the HLA region have been shown to be shared primarily with T1DM, rheumatoid arthritis (RA), Crohn's disease, and ulcerative colitis (UC).[8]

The prevalence of CD in first-degree relatives (FDRs) to individuals with CD is approximately 10%.[9–11] Despite these findings, little is known about the risk of nonceliac autoimmune disease in FDRs to individuals with CD. One earlier study of 1272 FDRs showed an increased risk of T1DM but not thyroid autoimmunity or RA.[12] Another smaller study showed that seemingly some autoimmune diseases were increased in 225 FDRs to CD children.[13] However, the statistical power in both earlier studies was limited. Hence, we aimed to assess the risk of several autoimmune diseases in celiac FDRs compared with matched control FDRs (age, sex, county, and calendar year) in a nationwide population-based longitudinal cohort study. We hypothesized that celiac FDRs, in comparison with control FDRs, would have an excess risk of nonceliac autoimmune disease.

Methods

Collection of Biopsy Data

Data regarding CD were collected in 2006 to 2008 through computerized duodenal/jejunal biopsies performed at all Swedish Pathology Departments between 1969 and 2008. CD was defined as having a biopsy specimen classified with villous atrophy equal to histopathology, stage Marsh III,[14] with date of first pathologic biopsy as the date of diagnosis and study entry. In total, there were 29,096 celiac individuals identified. Taking small intestinal biopsy samples is the clinical routine in Sweden,[15] and more than 95% of individuals with Marsh III changes have CD in a Swedish setting.[15]

Reference Individuals: Controls

By using the Swedish Total Population Register, all celiac individuals were matched with up to 5 reference individuals (controls) by the government agency Statistics Sweden.[16] In all, there were 144,522 controls matched for sex, county, age, and calendar year of birth. All controls entered the study on the same date as their matched celiac individual (the date of positive biopsy). Patients with CD and their matched controls have been described in detail.[17] Given the nationwide character of the study any individual selected as a control could have celiac FDRs. In this study about FDRs they were hence counted as control FDRs (with own CD).

First-Degree Relatives and Spouses

Through the Swedish Multi-Generation Register[18] we obtained data on all FDRs (father, mother, siblings, and offspring) to celiac individuals and controls; from the Total Population Register[16] we obtained data on all registered spouses (defined through marriage) (Figure 1). Spouses should represent genetically different individuals sharing the same environment as the celiac/index individuals. Because we did not have access to dates of marriage or lengths of marriage, a person who was at some point married to a person with CD was classified as a spouse. All FDRs and spouses entered the study on the same date of the corresponding index individual's study entry or at birth, whichever occurred latest (Figure 1). We defined exposure as being a celiac FDR or a celiac spouse. Celiac spouse was defined as a spouse to an individual with CD.

Outcome Measures

Different autoimmune diseases, in which either the highest reported prevalence exceeding 50 or reported incidence exceeding 5 per 100,000 individuals in Western countries with a previously reported association to CD, were selected as outcome measures. Included diseases were defined according to relevant International Classification of Diseases codes (Supplementary Table 1). For Addison's disease, the primary biliary cirrhosis, IgA deficiency, and chronic immune thrombocytopenia purpura prevalence figures were either approximately 15 to 25 per 100,000 individuals or unknown. We therefore calculated the incidence of these diseases in the Swedish Patient Register (containing inpatient and hospital-based outpatient data). Based on earlier data, the incidence in a control population of healthy individuals per 100,000 person-years was 7 for sarcoidosis,[19] 2 for IgA deficiency,[20] 1.5 for both Addison's disease[21] and chronic immune thrombocytopenia,[22] and 0.3 for primary biliary cirrhosis.[23] Given the high relative risk of sarcoidosis in

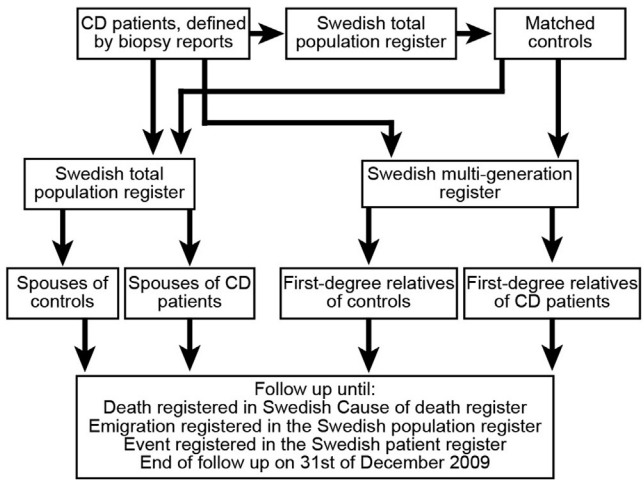

Figure 1. Linkage of registries.