Increased Risk of Cataract Among 28,000 Patients With Celiac Disease

Kaziwe Mollazadegan*, Maria Kugelberg, Birgitta Ejdervik Lindblad, and Jonas F. Ludvigsson

* Correspondence to Dr. Kaziwe Mollazadegan, Clinical Epidemiology Unit, Department of Medicine, Karolinska University Hospital, Building T2, Eugeniahemmet, SE-171 76 Stockholm, Sweden (e-mail: kaziwe.mollazadegan@live.se).

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Vitamin deficiencies are prevalent in celiac disease (CD) and are associated with cataract formation, but it is unknown whether persons with CD are at increased risk of cataract. The authors’ objective in this population-based cohort study was to determine the risk of cataract among persons with biopsy-verified CD. Data on CD were collected from reports on small intestinal biopsies performed between July 1969 and February 2008 in the 28 regional pathology departments in Sweden. The authors identified 28,756 persons with CD (villous atrophy, Marsh pathology stage 3). For each person with CD, Statistics Sweden selected up to 5 controls matched for age and sex from the Total Population Register. Data on cataract were obtained from the Swedish National Hospital Discharge Register and the National Day-Surgery Register. Cox regression analysis was used to estimate the risk of cataract. During a median follow-up period of 9 years, the authors identified 1,159 cataracts among persons with CD (909 were expected) (hazard ratio = 1.28, 95% confidence interval: 1.19, 1.36). The absolute risk of cataract was 397/100,000 person-years in CD, with an excess risk of 86/100,000 person-years. In conclusion, this study found an increased risk of developing cataract in patients with CD.

cataract; celiac disease; cohort studies; eye

Abbreviations: CD, celiac disease; CI, confidence interval; HR, hazard ratio; ICD, International Classification of Diseases.
Celiac disease

We defined CD as the presence of villous atrophy (Marsh pathology stage 3; see Web Table 1, which appears on the Journal’s Web site (http://aje.oxfordjournals.org/)) according to biopsy reports from any of the 28 regional pathology departments in Sweden (22). From October 2006 to February 2008, we collected data on biopsies performed between July 1969 and February 2008. Data collection was restricted to computerized biopsy reports. This explains why most of our patients were biopsied after 1990 (Table 1). Local information technology technicians carried out the computerized searches and delivered data including the dates of arrival of the biopsies at the pathology departments, each subject’s Personal Identity Number (23), morphology according to Swedish SnoMed classification codes (Web Table 1) (24), and topography of the duodenum or jejunum.

While the focus of the current study was biopsy-verified CD (villous atrophy), we also collected data on inflammation (Marsh stages 1–2) and normal mucosa (Marsh stage 0). We did not require positive CD serologic findings to establish a diagnosis of CD, but earlier validation has shown that 88% of persons with villous atrophy and available data on CD serology have positive CD serologic findings prior to biopsy (22). Throughout the study period, a small intestinal biopsy with villous atrophy was the gold standard for diagnosing CD, and 95% of persons with villous atrophy have CD (22). In Web Table 1, we present the Swedish SnoMed system used in the current study and how it compares with other histopathologic classifications, including that of Marsh (25). We used the same data set as in an earlier study of mortality among persons with CD (5).

After removing duplicates and biopsies with data irregularities (e.g., biopsies performed before birth or after the death of the patient), we had data from 351,403 biopsy reports in 287,586 unique individuals. For comparison, we also identified persons with inflammation without villous atrophy (n = 13,446) and those with a normal biopsy (n = 244,992). A subset of persons with normal mucosa were linked to positive CD serologic data from 8 university hospitals (24) to identify persons with potentially early CD (normal mucosa but positive CD serologic findings up to 180 days before biopsy and until 30 days after biopsy) (n = 3,736).

Records from biopsied persons (n = 46,330) were then sent for matching by the government agency Statistics Sweden. Statistics Sweden also replaced the Personal Identity Numbers with serial numbers to guarantee the anonymity of the study participants. We excluded 174 (0.4%) persons from all statistical analyses because their biopsy specimens may have been obtained from the ileum and another 35 persons because there were no available reference subjects or because serial numbers were missing. Of the remaining 46,121 persons with a biopsy result, 29,096 had CD. Additional exclusions are shown in Figure 1.

### Table 1. Characteristics of Participants in a Population-based Cohort Study on Celiac Disease and Risk of Cataract, Sweden, 1969–2008

<table>
<thead>
<tr>
<th></th>
<th>Matched Controls</th>
<th>CD Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>%</td>
<td>Median (Range) Mean (SD)</td>
</tr>
<tr>
<td>Total</td>
<td>142,036</td>
<td>28,756</td>
</tr>
<tr>
<td>Age at study entry, years</td>
<td>29 (0–95)</td>
<td>30 (0–95)</td>
</tr>
<tr>
<td>Attained age, years</td>
<td>42 (1–105)</td>
<td>42 (1–100)</td>
</tr>
<tr>
<td>0–19</td>
<td>58,808</td>
<td>11,795</td>
</tr>
<tr>
<td>20–39</td>
<td>26,339</td>
<td>5,305</td>
</tr>
<tr>
<td>40–59</td>
<td>31,955</td>
<td>6,427</td>
</tr>
<tr>
<td>≥60</td>
<td>24,934</td>
<td>5,229</td>
</tr>
<tr>
<td>Duration of follow-up, years</td>
<td>9 (0–40)</td>
<td>10.3 (6.4)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>88,001</td>
<td>17,790</td>
</tr>
<tr>
<td>Male</td>
<td>54,035</td>
<td>10,966</td>
</tr>
<tr>
<td>Calendar yearb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1969 or earlier</td>
<td>20,237</td>
<td>4,086</td>
</tr>
<tr>
<td>1990–1999</td>
<td>59,112</td>
<td>11,958</td>
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<tr>
<td>2000 or later</td>
<td>62,687</td>
<td>12,712</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>1,702</td>
<td>1,269</td>
</tr>
</tbody>
</table>

Abbreviations: CD, celiac disease; SD, standard deviation.

a Follow-up continued until diagnosis of cataract, death, emigration, or December 31, 2008. In reference subjects, follow-up could also end if the person underwent a small intestinal biopsy with CD, inflammation, or normal mucosa (in persons with positive CD serologic findings).

b Calendar year indicates the year of first biopsy and the start of follow-up.
Reference subjects

For each person with biopsy-verified CD, we identified up to 5 reference subjects matched for sex, age, county, and calendar year through the Total Population Register (26). Reference subjects were sampled from all Swedish residents for whom the 28 regional pathology registers had not indicated a previous duodenal/jejunal biopsy. Initially, Statistics Sweden identified 229,800 reference subjects. We first excluded 921 persons because they could not be matched to patients undergoing biopsy (due to a previous cataract diagnosis) and another 247 because of data irregularities. Of the remaining 228,632 controls, 144,522 had been matched to patients with CD. Additional exclusions are shown in Figure 1.

Outcome measures

We defined persons with cataract as those who either had a relevant International Classification of Diseases (ICD), Seventh to Tenth Revisions, code of cataract in the Swedish National Hospital Discharge Register or had undergone cataract surgery according to the Swedish National Day-Surgery Register (see Figure 2 for study overview) (Web Appendix 1). According to the Swedish National Cataract Register (2009 data), most patients undergoing cataract surgery were female (60.9%). The mean age for all patients was 74.9 years, and the median visual acuity in the surgically treated eye was 0.4 Snellen Decimal as compared with 0.7 Snellen Decimal in the healthy eye.

In Sweden, access to cataract surgery is high, and the mean waiting time for surgery is 2.9 months (2009 data). Nuclear opacities make up the most common subtype of cataract in older populations and in eyes undergoing cataract surgery (27).

Other covariates

We identified persons with type 1 diabetes through the Swedish Hospital Discharge Register. Earlier versions of the Swedish ICD (the Seventh to Ninth Revisions) did not distinguish between type 1 diabetes and type 2 diabetes. In the current study, type 1 diabetes was defined as a relevant ICD code (Seventh to Tenth Revisions) recorded before the age of 30 years. In a subanalysis, we also adjusted for education using 7 a priori educational categories determined by Statistics Sweden.

Statistical analyses

The hazard ratio for cataract was determined through Cox regression analysis. This model stratified data internally for age at the time of the first biopsy (corresponding age in reference subjects), calendar period, sex, and county and resembled conditional logistic regression analysis. Internal stratification eliminates the effect of all matching variables. Follow-up began on the date of the first positive biopsy (CD, inflammation, or normal mucosa (in a person in whom CD serology was positive at the time of biopsy)) or on the corresponding date in matched reference subjects. Follow-up time ended with a diagnosis of cataract, death, or emigration or on December 31, 2008, whichever occurred first. In reference subjects, follow-up could also end if the person underwent a small intestinal biopsy. The proportional hazards assumption was tested through log-minus-log curves.

We evaluated the risk of cataract according to duration of follow-up (<1, 1–<5, or ≥5 years), sex, age at first biopsy (0–19, 20–39, 40–59, or ≥60 years), and calendar period of the first biopsy (1989 or earlier, 1990–1999, or 2000 or later). Furthermore, incidence rates were calculated on the basis of the number of first cataract events divided by the number of person-years at risk.

In a subanalysis, we restricted our outcome to cataracts listed as the main diagnosis in the Swedish Hospital Discharge Register. In that subanalysis, we also restricted our outcome to those ICD cataract codes that were unlikely to have an external cause (i.e., we excluded cataracts due to trauma, infections, and pharmaceutical side effects; see Web Appendix 1).
In a separate analysis, we adjusted our data for education, because earlier research indicated relations between education, medical-care-seeking (and ascertainment of CD) (28), and lens opacity (29). We also adjusted for a diagnosis of type 1 diabetes, since this disease is associated with both CD (30) and cataract (31) and may also affect hospital admission patterns in patients with CD.

Cataracts occurring before age 50 years may have different phenotypes and genetic associations than the age-related cataracts occurring at older ages (32). Therefore, in a post-hoc analysis, we specifically examined the risk of cataract in persons aged 40–49 years and 50–59 years at study entry.

Internal comparison. To test whether an increased risk of cataract was specific to patients with CD (Marsh stage 3), we compared the risk of cataract in patients with CD with that in persons with a lesser degree of small intestinal histopathology, Marsh stages 1–2 (inflammation \( n = 12,955 \)) and Marsh stage 0 (normal mucosa but with positive CD serologic findings \( n = 3,672 \))).

Previous cataract and risk of CD. We used conditional logistic regression to calculate odds ratios for CD in patients with a previous cataract.

Statistical significance and power. Statistical significance was defined as 95% confidence intervals that excluded 1.0. We used SPSS 16.0 software (SPSS, Inc., Chicago, Illinois) to perform the analyses. Power analyses, using a 5% alpha level and 80% power, showed a detectable hazard ratio with respect to cataract of 1.10 for CD (calculated through STPlan, University of Texas M. D. Anderson Cancer Center).

Ethics

This project was approved by the Research Ethics Committee of the Karolinska Institutet (Stockholm, Sweden).

RESULTS

Background data

Most study participants were women (Table 1). The median age at first recorded cataract was 75 years in patients with CD and 76 years in controls (median durations from biopsy to cataract were 7 years in patients with CD and 8 years in controls). Other patient characteristics are shown in Table 1.

CD and subsequent cataract

During follow-up, we identified 1,159 cataracts among persons with CD; 909 were expected (hazard ratio (HR) = 1.28, 95% confidence interval (CI): 1.19, 1.36) (Table 2). The absolute risk (incidence) of cataract disease was 397/100,000 person-years in CD (expected: 311), with an excess risk of 86/100,000 person-years. The proportion of persons with cataract among patients with CD due to the underlying CD was 22% (Table 2). Adjustment for type 1 diabetes

or education did not change the risk estimates more than marginally (HR = 1.26 (95% CI: 1.18, 1.35) and HR = 1.26 (95% CI: 1.17, 1.36), respectively). Neither did the risk estimate change when we excluded the first year of follow-up (HR = 1.28, 95% CI: 1.20, 1.38).

The risk estimates were similar in women (HR = 1.23, 95% CI: 1.13, 1.33) and men (HR = 1.37, 95% CI: 1.22, 1.53). We found no interaction between CD and sex (P = 0.247). Risk estimates were also similar over calendar periods (Table 3). Few persons biopsied before the age of 20 years had sufficient follow-up to be at risk of cataract. This explains the low number of cataracts (n = 12) in that group, and although the HR was 1.56, it was not statistically significant (Table 3). Among patients biopsied after the age of 40 years, the hazard ratio for cataract was 1.2–1.3.

When we restricted our outcome to persons admitted to a hospital with a main diagnosis of cataract according to a narrower definition of cataract (Web Appendix 1), persons with CD had a 1.8-fold increased risk of cataract (HR = 1.81, 95% CI: 1.40, 2.36).

In a post-hoc analysis, we found an increased risk of later cataracts both in persons diagnosed with CD at age 40–49 years (HR = 1.40, 95% CI: 1.11, 1.77; 94 observed cataracts in persons with CD) and in persons diagnosed at ages 50–59 years (HR = 1.23, 95% CI: 1.05, 1.43; 207 observed cataracts in persons with CD).

Comparison with other persons undergoing small intestinal biopsy

Persons with CD were at a slightly lower risk of cataract than persons with inflammation (HR = 0.95, 95% CI: 0.87, 1.04) but at a higher risk than persons with normal mucosa and positive CD serologic findings (HR = 1.09, 95% CI: 0.89, 1.34) (results were adjusted for sex, age at biopsy, and calendar period). However, none of these associations reached statistical significance.

Risk of CD in patients with previous cataract

Patients with a previous cataract were at a slightly increased risk of later CD (odds ratio = 1.14, 95% CI: 1.02, 1.30).

DISCUSSION

To the best of our knowledge, this is the first large-scale, population-based study of CD and the risk of cataract. We found a moderately increased risk of cataract development in persons with biopsy-verified CD. The risk estimates were similar in women and men. Adjustment for type 1 diabetes and education did not change our risk estimates.

There are several potential explanations for an association between CD and cataract. First, cataract is associated with vitamin deficiencies, and although research is inconsistent (33–35), some studies have suggested that vitamin supplementation protects against cataract formation (14–16). Vitamin deficiencies are prevalent in both undiagnosed CD (due to malabsorption or ongoing intestinal inflammation) and diagnosed CD (a gluten-free diet may not contain sufficient amounts of certain vitamins) (36, 37). Validation of a subset of patients with biopsy-verified CD found that 22% of patients had folate deficiency and 14% had vitamin B12 deficiency (22).

Second, oxidative stress is important in the development of cataract (11–13) and has also been linked to CD (8–10). Research suggests that gluten interrupts the antioxidant/proxidant balance in the intestinal mucosa, causing a reduction in the antioxidant capacity of CD patients both in the mucosa and in peripheral blood, leading to a disruption of tissue homeostasis and therefore causing complications in CD, such as malignancies.

Third, our findings may be explained by shared risk factors for CD and cataract, since prior cataract was also linked to CD. CD is an autoimmune disease, and cataract has previously been linked to other autoimmune diseases, including type 1 diabetes (20). It has even been suggested that cataract itself is an autoimmune disorder (21). Furthermore, other studies have shown that inflammation may induce cataract development. It may be that the disease patterns of CD and cataract share similar immunologic and autoimmune properties. The positive association between CD and cataract before CD diagnosis could also be due to inflammation preceding the diagnosis. Studies have shown that undiagnosed CD is associated with complications as well (38, 39).

Finally, some of the increased risk for cataract may be due to surveillance bias, that is, increased surveillance of patients with CD. However, the consistent increase in cataract risk even more than 5 years after the first biopsy, in combination with no change in risk estimates after exclusion of the first year of follow-up, argues against surveillance bias being the only explanation for our findings.

This nationwide study had several strengths. Through our unique population-based ascertainment of cases with CD, we minimized selection bias. Although the diagnostic

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**Table 2. Risk of Cataract Among Patients With Celiac Disease, According to Duration of Follow-up, Sweden, 1969–2008**

<table>
<thead>
<tr>
<th>Duration of Follow-up (years)</th>
<th>No. of Observed Events</th>
<th>No. of Expected Events</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
<th>Absolute Risk/100,000 PYAR</th>
<th>Excess Risk/100,000 PYAR</th>
<th>Attributable %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1,159</td>
<td>909</td>
<td>1.28</td>
<td>1.19, 1.36</td>
<td>&lt;0.001</td>
<td>397</td>
<td>86</td>
<td>22</td>
</tr>
<tr>
<td>&lt;1</td>
<td>73</td>
<td>63</td>
<td>1.17</td>
<td>0.90, 1.51</td>
<td>0.238</td>
<td>257</td>
<td>37</td>
<td>14</td>
</tr>
<tr>
<td>1–4.9</td>
<td>383</td>
<td>261</td>
<td>1.47</td>
<td>1.31, 1.65</td>
<td>&lt;0.001</td>
<td>378</td>
<td>121</td>
<td>32</td>
</tr>
<tr>
<td>≥5</td>
<td>703</td>
<td>589</td>
<td>1.19</td>
<td>1.09, 1.30</td>
<td>&lt;0.001</td>
<td>432</td>
<td>70</td>
<td>16</td>
</tr>
</tbody>
</table>

Abbreviation: PYAR, person-years at risk.

a The reference group was the general population comparator cohort.
The criteria for CD have changed over time, small intestinal biopsy was a prerequisite for diagnosis of CD in Sweden throughout the study period. Earlier validation also showed that more than 95% of Swedish gastroenterologists and pediatricians perform a small intestinal biopsy before diagnosing CD (22). Patient chart reviews have shown that 95% of patients with villous atrophy have CD (22). In fact, misclassification of CD in the current study is likely to have been lower than in the Swedish Hospital Discharge Register, where the positive predictive value for CD is 85%, as compared with 95% in our study (40).

Another strength of this study was our use of secondary reference groups. However, compared with persons with a lesser degree of histopathologic abnormality (Marsh stages 1–2 and Marsh stage 0), patients with CD (villous atrophy) were at no increased risk of cataract. From that analysis, we conclude that the increased risk of cataract is probably independent of histopathology of the small intestine in CD.

In this study, as well as in others carried out by our research group (41–43), we defined cataract according to relevant ICD codes. We had no data on standardized ocular examinations or data on cataract subtypes among our patients. Still, restricting our outcome to cataract surgery did not change our risk estimates. When we used a narrow definition of cataract, the hazard ratios increased slightly, suggesting that the hazard ratio for cataract in CD may be even higher than 1.28.

We had no information on patient weight and height, smoking, ultraviolet light exposure, alcohol use, or vitamin supplementation in our analyses. However, data from previous studies suggest that smoking is positively associated with cataract (41) but inversely related to CD (44). If persons with CD are less likely to smoke, there is a risk that the current study underestimated the association between CD and cataract. While obesity is positively associated with cataract (45), it is inversely related to CD (46). Furthermore, we did not adjust for the use of steroids, which is associated with cataract formation; however, since there is no pharmalogic treatment for CD available today, the lack of adjustment for steroid treatment cannot explain our results. Thus, although residual or unmeasured confounding remains a possible explanation for our results, the most likely effect of our lack of adjustment for these factors is underestimation of the true hazard ratios. This was further corroborated by linkage of our data with data from the nationwide Swedish Medical Birth Registry (47), in which the prepregnancy body mass index and smoking behavior of almost all Swedish women subsequently giving birth are registered. We had data on these parameters for 2,541 women with CD and 12,199 without CD. As we suspected, women with CD were less likely to be smokers (18.3% vs. 20.2%) and less likely to be overweight/obese (23.2% vs. 31.1%).

In conclusion, we found a moderately increased risk of cataract in persons with biopsy-verified CD. We suggest that this association is due to shared risk factors for the 2 conditions.

**ACKNOWLEDGMENTS**

Author affiliations: Clinical Epidemiology Unit, Department of Medicine, Karolinska University Hospital, Solna, Sweden (Kaziwe Mollazadegan, Jonas F. Ludvigsson); St. Erik Eye Hospital, Karolinska Institutet, Stockholm, Sweden (Maria Kugelberg); Department of Ophthalmology,

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**Table 3. Risk of Cataract Among Patients With Celiac Disease in Subgroup Analyses, Sweden, 1969–2008**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Observed Events</th>
<th>No. of Expected Events</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
<th>Absolute Risk/100,000 PYAR</th>
<th>Excess Risk/100,000 PYAR</th>
<th>Attributable %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>422</td>
<td>308</td>
<td>1.37</td>
<td>1.22, 1.54</td>
<td>&lt;0.001</td>
<td>384</td>
<td>104</td>
<td>27</td>
</tr>
<tr>
<td>Female</td>
<td>737</td>
<td>599</td>
<td>1.23</td>
<td>1.13, 1.33</td>
<td>&lt;0.001</td>
<td>404</td>
<td>76</td>
<td>19</td>
</tr>
<tr>
<td><strong>Age at first biopsy, years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>12</td>
<td>8</td>
<td>1.56</td>
<td>0.82, 2.99</td>
<td>0.178</td>
<td>9</td>
<td>3</td>
<td>36</td>
</tr>
<tr>
<td>20–39</td>
<td>49</td>
<td>20</td>
<td>2.47</td>
<td>1.75, 3.50</td>
<td>&lt;0.001</td>
<td>90</td>
<td>54</td>
<td>60</td>
</tr>
<tr>
<td>40–59</td>
<td>301</td>
<td>236</td>
<td>1.28</td>
<td>1.12, 1.45</td>
<td>&lt;0.001</td>
<td>447</td>
<td>97</td>
<td>22</td>
</tr>
<tr>
<td>≥60</td>
<td>797</td>
<td>648</td>
<td>1.23</td>
<td>1.13, 1.34</td>
<td>&lt;0.001</td>
<td>2,209</td>
<td>413</td>
<td>19</td>
</tr>
<tr>
<td><strong>Calendar year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1989 or earlier</td>
<td>256</td>
<td>186</td>
<td>1.38</td>
<td>1.18, 1.60</td>
<td>&lt;0.001</td>
<td>318</td>
<td>88</td>
<td>28</td>
</tr>
<tr>
<td>1990–1999</td>
<td>580</td>
<td>472</td>
<td>1.23</td>
<td>1.12, 1.35</td>
<td>&lt;0.001</td>
<td>394</td>
<td>74</td>
<td>19</td>
</tr>
<tr>
<td>2000 or later</td>
<td>323</td>
<td>250</td>
<td>1.29</td>
<td>1.14, 1.47</td>
<td>&lt;0.001</td>
<td>500</td>
<td>113</td>
<td>23</td>
</tr>
</tbody>
</table>

Abbreviation: PYAR, person-years at risk.

a The reference group was the general population comparator cohort.

b Calendar year indicates the year of first biopsy and the start of follow-up.

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REFERENCES


