# Risk of cutaneous malignant melanoma in patients with celiac disease: A population-based study

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***Background:*** Celiac disease (CD) carries an increased risk of several malignancies, including cancers of the gastrointestinal tract and hematologic malignancies. The disease course of cutaneous malignant melanoma (CMM) is affected by the immune status of the host, and therefore may be associated with CD.

***Objective:*** We sought to test for an association between CD and CMM in a population-based setting.

***Methods:*** We queried all (n = 28) pathology departments in Sweden and identified patients with intestinal histology consistent with CD. Each patient was matched to up to 5 control subjects by age, gender, calendar period, and region. Using Cox proportional hazards, we tested for an association between CD and the subsequent diagnosis of CMM.

***Results:*** Among patients with CD (n = 29,028), 78 subsequently developed CMM (0.3%). Compared with control subjects there was no significant association between CD and CMM (hazard ratio 0.94, 95% confidence interval 0.73-1.20). This null association was similar for men (hazard ratio 0.99, 95% confidence interval 0.68-1.44) and women (hazard ratio 0.89, 95% confidence interval 0.64-1.24), and in all age strata.

***Limitations:*** Lack of data regarding undiagnosed CD is a limitation.

***Conclusion:*** In this population-based study we found no association between CD and the subsequent diagnosis of CMM. Prior studies showing a positive association between these 2 entities may have been a result of referral bias. (J Am Acad Dermatol 2014;71:245-8.)

***Key words:*** celiac disease; melanoma.

Celiac disease (CD) is a chronic, immune-based disorder that is triggered by the ingestion of gluten in genetically susceptible individuals.[1] Patients with CD have an increased risk of developing certain malignancies including lymphoma and small-intestinal adenocarcinoma.[2-5]

There is uncertainty regarding the risk of cutaneous malignant melanoma (CMM) in patients with CD. Two studies showed no association between CMM and CD[6,7] whereas a third study found a significant association.[4] Both conditions

*Abbreviations used:*

| | |
|---|---|
| CD: | celiac disease |
| CI: | confidence interval |
| CMM: | cutaneous malignant melanoma |
| HR: | hazard ratio |

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have been increasing in incidence over the past few decades.[8,9]

Given the contradictory epidemiologic data on the relationship between these 2 conditions, their relationship with the immune system, and their parallel increasing incidences, we aimed to quantify the association between CD and the subsequent diagnosis of CMM in a population-based cohort study.

**CAPSULE SUMMARY**

- The literature regarding the risk of cutaneous malignant melanoma in patients with celiac disease is conflicting.
- In this population-based study, we found no increased risk of cutaneous malignant melanoma in patients with celiac disease.
- These results suggest that no additional screening for melanoma is warranted in patients with celiac disease.

## METHODS

### Identification of cases and controls

We identified patients with histologic evidence of CD at all 28 pathology departments in Sweden from July 1969 to February 2008. CD was defined via Systematized Nomenclature of Medicine-Clinical Terms (SnoMed) codes corresponding to villous atrophy. In a previous validation study involving medical record review of 114 patients with villous atrophy identified through this method, 95% had a clinical diagnosis of CD.[10] Each patient with CD was then matched via the Total Population Register to up to 5 non-CD control subjects, using the following matching parameter: age, gender, year, and region within Sweden.

### Measured outcomes

All patients with CD (n = 29,096) and control subjects (n = 144,522) were cross-referenced with the population-based Swedish Cancer Registry,[11] and cases of CMM were identified based on the *International Classification of Diseases, Revision 7* code 190.x. We excluded all individuals who received a diagnosis of CMM before CD diagnosis (n = 68) or the corresponding date of inclusion as a control (n = 466). We also recorded, when available, whether the patient was given the diagnosis of in situ CMM versus invasive CMM. In the case of individuals who were coded for both in situ and invasive CMM, we classified such patients as having whichever diagnosis came later, because reclassification was likely as a result of further histologic review.

### Statistical considerations and sensitivity analyses

Time at risk began on the day of CD diagnosis or the corresponding date of inclusion as a control, and patients were followed up until the development of CMM, death, emigration, or December 31, 2009. We used Cox proportional hazards, conditioned on sex, age, calendar period, and region to measure for an association between CD and the subsequent development of CMM. We also separately calculated the degree of association between CD and in situ CMM and invasive CMM. In these analyses, we adjusted for educational attainment; in the case of children, we used the greater educational attainment of the 2 parents.

Because the risk of certain malignancies and mortality in CD changes over time,[2,12] we subsequently used pseudo-time-dependent covariates to test whether the relationship between CD and CMM remained constant over time after CD diagnosis. We then performed stratified analyses based on age group (0-19, 20-39, 40-59, and ≥ 60 years), gender, and calendar period so as to determine whether the relationship between CD and CMM was modified by any of these parameters.

In a series of sensitivity analyses, we retested for an association between CD and CMM, now: (1) no longer adjusting for educational attainment; (2) excluding any patient with malignant melanoma diagnosed during the first year after CD diagnosis, and starting time at risk 1 year after diagnosis; and (3) excluding any patient with any solid organ or hematologic malignancy before CD diagnosis.

We used software (SAS, Version 9.3, SAS Institute Inc, Cary, NC) for all analyses. We report hazard ratios (HR) with corresponding 95% confidence intervals (CI), and all reported *P* values are 2-sided. The research ethics committee of the Karolinska Institute approved this study (2006/633-31/4) on June 14, 2006.

## RESULTS

Characteristics of patients with CD and matched control subjects are shown in Table I. The median age of CD diagnosis was 30 years. Some 62% of patients were female and the majority of patients were given the diagnosis of CD after 1990. The median follow-up time for patients with CD and control subjects was 9.9 years and 10.1 years, respectively. During the follow-up, 78 (0.3%) patients with CD and 427 (0.3%) control subjects developed CMM.

Among the 78 patients with CD who then developed CMM, the median time that elapsed between CD diagnosis and CMM was 7.7 years

**Table I.** Characteristics of patients with celiac disease and matched control subjects

| Characteristic | CD, n = 29,028 (%) | Control, n = 144,056 (%) |
|---|---|---|
| Age at study entry, y | | |
| 0-19 | 11,801 (41) | 58,852 (41) |
| 20-39 | 5306 (18) | 26,353 (18) |
| 40-59 | 6452 (22) | 32,081 (22) |
| ≥ 60 | 5469 (19) | 26,770 (19) |
| Male | 11,064 (38) | 54,776 (38) |
| Female | 17,964 (62) | 89,280 (62) |
| Calendar period of study entry | | |
| ≤ 1989 | 4101 (14) | 20,333 (14) |
| 1990-1999 | 12,033 (41) | 59,691 (41) |
| ≥ 2000 | 12,894 (44) | 64,032 (44) |
| Median/mean follow-up time, y | 9.9/11.2 | 10.1/11.4 |
| Developed CMM | 78 (0.3) | 427 (0.3) |

*CD*, Celiac disease; *CMM*, cutaneous malignant melanoma.

(range 0.3-24.9 years). Among patients with CD, the median age at CMM diagnosis was 60.1 years (range 18.8-87.6 years).

Overall there was no significant association between CD and CMM (HR 0.94, 95% CI 0.73-1.20) (Table II). This null relationship remained stable over time (<1 year since CD diagnosis: HR 0.57, 95% CI 0.20-1.62; 1-5 years: HR 0.88, 95% CI 0.54-1.42; >5 years: HR 1.01, 95% CI 0.75-1.36). On repeated analysis, now not adjusting for level of education, the null relationship persisted (HR 0.94, 95% CI 0.73-1.20). In a sensitivity analysis excluding any patient with CMM diagnosed during the first year after CD diagnosis, and starting the at-risk time 2 years after diagnosis or inclusion as a control, the relationship remained null (HR 0.97, 95% CI 0.75-1.25). Similarly, when we repeated the analysis, now excluding patients with any malignancy before CD diagnosis or exclusion as a control, the relationship remained null (HR 0.96, 95% CI 0.75-1.24).

The null relationship between CD and subsequent diagnosis of malignant melanoma was similar for men (HR 0.99, 95% CI 0.68-1.44) and women (HR 0.89, 95% CI 0.64-1.24). There did not appear to be effect modification according to age of CD diagnosis; although the CI were wide for those younger than 20 years (when restricted to those >60 years: HR 2.03, 95% CI 0.70-5.89), there was no significant association between CD and CMM in any of the predetermined age strata. When stratifying by year of CD diagnosis, the null association was present in all 3 time strata: before 1989 (HR 0.73, 95% CI 0.40-1.33), 1990 to 1999 (HR 0.89, 95% CI 0.62-1.27), and 2000 and after (HR 1.16, 95% CI 0.76-1.77). When analyzing in situ CMM and invasive CMM separately we found that neither in situ CMM (HR 0.89, 95% CI 0.55-1.44) nor invasive CMM (HR 0.93, 95% CI 0.70-1.25) was increased in patients with CD.

**Table II.** Association of celiac disease with cutaneous malignant melanoma stratified by follow-up time

| Stratum | No. of events | Adjusted* HR (95% CI) | *P* value |
|---|---|---|---|
| Overall | | | |
| Control | 427 | 1.0 | |
| Celiac disease | 78 | 0.94 (0.73-1.20) | .6018 |
| <1 y | | | |
| Control | 36 | 1.0 | |
| Celiac disease | 4 | 0.57 (0.20-1.62) | .2932 |
| 1-5 y | | | |
| Control | 113 | 1.0 | |
| Celiac disease | 20 | 0.88 (0.54-1.42) | .6036 |
| >5 y | | | |
| Control | 278 | 1.0 | |
| Celiac disease | 54 | 1.01 (0.75-1.36) | .9477 |

*CI*, Confidence interval; *HR*, hazard ratio.
*Adjusted for education level.

## DISCUSSION

In this population-based cohort study of 29,028 patients with CD, we found no increased risk of developing CMM after a CD diagnosis as compared with matched control subjects. This lack of a significantly increased risk was noted in multiple time strata after CD diagnosis, and was similar across gender and age categories.

Previous studies investigating the relationship between CD and CMM have yielded conflicting results. In a population-based study of 869 patients with CD in England, United Kingdom, followed up from 1978 through 2001, only 1 case of CMM developed in the peridiagnosis period and none developed beyond 2 years after CD diagnosis.[7] In a Swedish study involving 11,019 inpatients with a diagnosis of CD, 4 developed CMM, which was not significantly different from the expected rate (standardized incidence ratio 0.6, 95% CI 0.2-1.7).[6] However, the CI were wide, leaving open the possibility of a modest positive association between these 2 conditions. One study of 381 patients with CD in the United States showed a strong positive association, with a standardized morbidity ratio of 5.0 (95% CI 2.1-12), although the setting of this positive study was in a referral center, and included cases of CMM that were diagnosed before the diagnosis of CD. The current study, involving 29,028 patients with CD free of CMM at the time of

CD diagnosis, is the largest investigation to date to our knowledge. The null findings are concordant with those of the 2 smaller population-based studies,[6,7] suggesting that the 1 positive study may have been influenced by referral bias.

Both CD and CMM share Caucasian race as a risk factor,[13,14] and both conditions have been increasing in incidence in recent decades. One study found that the seroprevalence of CD increased from 0.2% in the years spanning 1948 to 1954 to 0.9% in 2006 to 2008.[9] The increase in CMM incidence in recent decades has been documented in both the United States and Sweden,[8] although this increase is most marked among individuals older than 60 years; behavioral factors such as tanning could explain the increasing incidence of CMM in this age group.[13]

The role of the immune system in CMM has been the subject of extensive research.[15,16] Ipilimumab, a monoclonal antibody that blocks cytotoxic T-lymphocyte-associated antigen 4, is the first drug to show a modestly increased survival in patients with metastatic CMM.[17] This drug commonly causes gastrointestinal toxicity including enterocolitis[18] and in 1 case report, caused severe diarrhea that ultimately led to a new diagnosis of CD.[19] Although it is not known whether ipilimumab triggered the development of CD or merely exacerbated a subclinical form of this condition, the shared immune basis of CD and CMM prompted us to investigate the relationship between these 2 illnesses.

Strengths of this study include its population-based setting and large sample size, which permitted us to examine subgroups. The long follow-up time (median of 9.9 years) allowed us to determine whether a diagnosis of CD affected CMM in this time horizon, although there is a possibility that a risk confined to the long-term could be present. A limitation is that we were unable to determine whether undiagnosed CD (and thus ongoing gluten exposure) is associated with an increased risk of CMM.

In conclusion, we found no association between a diagnosis of CD and the subsequent development of CMM. These findings confirm those of smaller population-based studies testing for this association, and suggest that a previous positive study was likely influenced by referral bias. Although these 2 conditions share Caucasian race as a risk factor, CD itself does not appear to increase the risk of CMM and therefore no additional screening measures for CMM are warranted in these patients.

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