

## Geographic trends and risk of gastrointestinal cancer among patients with celiac disease in Europe and Asian-Pacific region

Mohammad Rostami Nejad<sup>1</sup>, David Aldulaimi<sup>2</sup>, Sauid Ishaq<sup>3</sup>, Mohammad Javad Ehsani-Ardakani<sup>1</sup>, Mohammad Reza Zali<sup>1</sup>, Reza Malekzadeh<sup>4</sup>, Kamran Rostami<sup>5</sup>

<sup>1</sup>Gastroenterology and Liver Diseases Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>2</sup>Department of Gastroenterology, Alexandra Hospital, Worcestershire, United Kingdom

<sup>3</sup>Gastroenterology Department, Dudley Group of Hospital, Dudley, United Kingdom

<sup>4</sup>Digestive Disease Research Institute, Tehran University of Medical Science, Tehran, Iran

<sup>5</sup>Department of Gastroenterology, Luton & Dunstable Hospital NHS Foundation Trust, Luton, United Kingdom

### ABSTRACT

Celiac disease is an autoimmune disorder that affects genetically predisposed individuals upon the ingestion of gluten. It is now considered one of the most common genetic disorders in Europe and Asian Pacific region with a prevalence of up to 2.67% of the population. The true prevalence of celiac disease may still be underestimated. Studies remain limited by sample size and selection bias. Celiac disease predisposes to the development of gastrointestinal malignancies, especially lymphomas and small bowel adenocarcinoma. The risk of developing a celiac disease associated malignancies remains uncertain, despite numerous studies. In Middle Eastern countries, the literature regarding celiac disease has expanded significantly in recent years. These studies reported have largely concentrated on the epidemiology of Celiac disease and there is an absolute and relative paucity of published research regarding celiac disease associated malignancy. The aim of this article is to review the current literature and evaluate the risk of gastrointestinal malignancies among patients with celiac disease and then review studies from the Asian Pacific region of the world.

**Keywords:** Celiac disease, Lymphoma, Adenocarcinoma, Europe, Asian Pacific region.

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### Risk of cancer in celiac disease patients

It is widely accepted that the risk of developing certain malignancies is increased in specific patient populations compared to the general population. This increased risk can be due to genetic or environmental factors, such as a family

history of bowel cancer or exposure to cigarette smoke. It can also be due to the development of conditions that predispose to the development of malignancies, such as inflammatory bowel disease and chronic hepatitis B infection. Celiac disease (CD) is an autoimmune disorder that affects genetically predisposed individuals upon the ingestion of gluten. It is now considered one of the most common genetic disorders in Europe and Asian Pacific region with a prevalence of up to 2.67% of the population (1-4). Numerous studies, typically reporting cases series, suggest that CD predisposes to both non-Hodgkin and an

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**Reprint or Correspondence:** Mohammad Javad Ehsani Ardakani, MD. Gastroenterology and Liver Diseases Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

**Email:** mjehsani@yahoo.com.

enteropathy associated T-cell lymphomas (NHL and EATL), specific to CD. Case series also suggest that CD also predisposes to small intestine adenocarcinoma, esophageal and oropharyngeal carcinomas (5-16). The mechanism(s) responsible for this predisposition remain uncertain but proposed mechanisms include increased intestinal permeability for ingested carcinogens, chronic inflammation, an impaired immune system and nutritional deficiencies (8). In this paper we will firstly review studies from European populations and then speculate regarding the risk of malignancy among patients with CD from the Asian and Pacific region, despite an absolute and relative paucity of literature regarding this important topic.

### Risk of gastrointestinal cancer in patients with celiac disease from Western studies

The majority of the studies regarding CD and malignancy indicate that the risk of gastrointestinal (GI) cancer in patients with CD is higher than the general population (8-15). This increased risk relates particularly to Non Hodgkin's lymphoma (NHL), enteropathy associated T-Cell lymphoma EATL and adenocarcinoma affecting the small intestine (5-16). Most of these studies report incidences affecting two distinct populations. One population is patients already known to have CD and is subsequently diagnosed with a malignancy. A second, and very different population, are patients diagnosed with CD as part of their assessment - after being diagnosed with a malignancy such as a gastrointestinal lymphoma.

### Malignancy in patients with known celiac disease

CD predisposes to lymphoma and gastrointestinal cancers. We will consider studies regarding lymphomas and then studies regarding

other gastrointestinal malignancies, although some studies overlap.

#### *Lymphoma in patients with known celiac disease*

Despite a relatively large number of publications regarding CD associated malignancy the risk of lymphoma reported varies widely. Studies report a relative risk varying from 1 (no greater than the general population for certain types of lymphoma) to a 300-fold relative increase in risk (17-19). This risk has varied over time. Recent studies suggest that the risk of lymphoma may be lower than originally reported, greatest in elderly patients and persisting for many years after initial diagnosis, even after adherence to a gluten free diet (6, 7, 20-23).

Studies have estimated the lifetime risk for a GI malignancy as between 1.3 and 2 percent for patients with CD (8, 10, 16, 22-25) (Table 1). In an initial study by Swinson in 1983, 113 of 235 confirmed CD associated malignancies were lymphomas, predominantly affecting the small intestine (among the remaining malignancies, there were 19 adenocarcinomas in the small-intestine) (23). Grainge et al. reported that the risk of any malignancy in CD patients compared with the general population was increased by 40%. Non-Hodgkin's lymphomas were detected in 14 patients, resulting in an overall incidence of 1.3 per 1000 person-years. The increased risk for all malignancies persisted for up to 15 years after diagnosis. The increased risk of non-Hodgkin's lymphoma remained raised compared to the general population for beyond 15 years (25). Goldacre et al. reported a population-based cohort study from the United Kingdom. This showed that the relative risk ratio for cancer in CD patients was 1.16. The highest relative risk related to non-Hodgkin's lymphoma (3.28) (26). A population-based study, reported by Askling et al, reported a series of 11,019 individuals with CD and dermatitis herpetiformis and reported a small increase in the risk of lymphoma (6).

**Table 1.** CD and risk of lymphomas in different studies

Country	CD cases, (N)	Lymphoma cases, (N)	Study period	References
United Kingdom (different studies)	8125	133	1963-2001	5, 17, 35, 39, 51
Italy (different studies)	260	679	1982-2005	11, 26, 56
Denmark and Sweden	28	3055	Denmark 2000-2002, Sweden 1999-2002	57
10 European countries	66	1446	1998-2001	38
Sweden (different studies)	12075	11084	1970-2000	13, 58
Spain	4732	23	1987-2002	37
USA (different studies)	1617	302	1996-2000	8, 19
South East of Asia	0	38	1990-2008	50

Ongoing inflammation may play a key role in the development of lymphoma. The recent study by Ludvigsson et al. show an increased risk of lymphoma among patients with CD, but only for patients with biopsy proven small bowel inflammation, and there was no increased risk for positive CD antibodies without duodenal histological damage compared to the general population (21). In keeping with this study Lohi et al. (27) and Godfrey et al. (28), reported results that support this study, but via different methodology. Using stored sera from a general population they measured CD specific auto-antibodies for evaluate the malignancy risk for undiagnosed CD. They reported a 1% prevalence of CD, but no increased mortality was found compared to serologically negative subjects.

#### ***Non-lymphomatous malignancies in patients with known celiac disease***

Patients with CD are also at increased risk of non-lymphomatous malignancies. A study of 4.5 million US veterans was reported by Landgren et al. (29). This series reported a relative risks was between 0.85 and 2.27 percent for the GI cancers, such as small bowel adenocarcinoma, associated with CD and also confirmed that other autoimmune diseases predispose to GI malignancies. A study by Green et al. reported on the outcome of 381 patients with CD, investigated between 1981 and 2000. The result of this study showed that 43

(11%) were diagnosed with malignancy. Nine malignancies were diagnosed after the diagnosis of CD, 7 were simultaneous diagnosis, and 27 malignancies were diagnosed before the diagnosis of CD. The authors concluded that patients with CD are at increased risks of small intestinal adenocarcinoma, esophageal cancer, melanoma, and non-Hodgkin's lymphoma. Furthermore the authors suggest that their study implied that the increased risk of a GI lymphoma persisted after the institution of a GFD (9). Askling et al. reported a similar study that suggested patients with CD have an increased risk of esophageal and pharyngeal carcinomas, and the analysis of cancer incidence in this cohort confirmed an increased risk of oropharyngeal malignancies (6). A study based in Italy in 2007 confirmed that patients with CD have an increased risk of malignancy and suggested that this risk increase with age at time of diagnosis of CD (30).

Other studies have been less conclusive. Using data from cohorts of patients with celiac disease, biopsy specimens were evaluated at 28 pathology centers in Sweden. Of these patients, 372 developed incident GI cancers; 347 patients with inflammation and 38 with latent CD developed GI cancers. This suggests that although the risk of GI cancers is increased in the first year after diagnosis of CD, but there is no increase in risk subsequently (8). Similarly, in a cohort study of

the mortality for patients with undetected coeliac disease compared with the general population, death due to cancer and circulatory diseases was not increased in 87 CD patients (31). In a Finnish population-based adult-representative cohort, 202 (2.9%) of the participants were tTG positive and 73 (1.1%) were EMA positive and the results showed that overall risk of malignancy was not increased among antibody-positive cases in the follow-up of two decades compared to tTG and EMA negative controls. Using these findings the authors suggest that there is no need for mass screening and early diagnosis of coeliac disease to prevent malignancy (32). This conclusion was supported by a study reported by Elli et al. This recently published study concluded that undiagnosed coeliac patients appear to have the identical risk of developing GI lymphomas as the general population and this risk seems not to be influenced by gluten exposure (30). Lebwohl et al. suggested that patients with positive CD serology did not have an increased risk of developing colonic adenomas compared to the general population (33). Perhaps of as much interest as studies reporting an increased risk of malignancy associated with CD are studies that suggest that CD may reduce the likelihood of developing certain malignancies; obesity predisposes to certain malignancies. CD may reduce the likelihood of developing obesity and women with CD may be at a reduced risk of breast cancer and gynecological malignancies (34, 35). Table 1 showed the prevalence of CD and lymphomas in different studies.

## Celiac disease in patients diagnosed with malignancy

### *CD in patients diagnosed with lymphoma*

As for series looking at the incidence of lymphoma in patients with CD, different series have reported markedly different rates of CD among

patients initially diagnosed with lymphoma localized to the GI tract and then subsequently investigated for CD. The prevalence of undiagnosed CD in GI non-Hodgkin's lymphoma ranges from 0% in studies conducted in Spain and Turkey to 2% in the study by Catassi et al. (11, 36, 37).

A case control study from Italy reported on the results of 653 patients with newly diagnosed NHL who, as part of their assessment following a diagnosis of NHL, were screened using the IgA class EMA antibody for CD (11). CD was diagnosed in 6 patients (0.92%). The lymphomas in this series consisted 3 cases of B-cell and 3 cases of T-cell origin. Four cases had lymphoma primarily located in the gut. Their study suggested that the CD-associated population attributable risk of NHL is very low. In contrast, Mearin et al. investigated the frequency of CD in patients that had been diagnosed with NHL compared to the general population, in 10 European countries (38). The study reported finding for 1446 consecutive patients with newly diagnosed NHL. The control group consisted of a population of 9676 individuals who were screened for CD. The result of this large cohort survey showed that patients with CD had a significantly increased risk of developing NHL, although lower than previously thought (38).

## Celiac disease in patients diagnosed with small bowel adenocarcinoma

Few Western studies have investigated the prevalence of CD among patients diagnosed with small bowel adenocarcinoma. In 2003 Howdle et al. reported the results of a postal survey regarding small bowel adenocarcinoma from members of the British Society of Gastroenterology (39). The study reported on 175 cases of small bowel adenocarcinoma, CD was diagnosed in 13 % of cases. This cohort included patients already known to have CD and cases diagnosed with CD after diagnosis of small bowel adenocarcinoma.

## Malignancy in children with celiac disease

Few studies have investigated whether children with CD have an increased risk of cancer. An international survey among members of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) described 22 new cases with both CD and cancer in children in Europe. In this group, there were more intestinal lymphomas and thyroid carcinoma than would be expected (40). Solaymani-Dodaran et al. evaluated 285 children diagnosed with celiac disease and followed them until death (24). The risk of malignancy was increased compared to the general population. These studies suggest that children with CD have an increased risk of malignancy compared to the general population.

## Geographical trend of celiac disease in the Asian-Pacific region and Europe

The incidence of CD varies widely among countries of the Asian-Pacific region compare to European countries. It is relatively common in Iran, Northern India and Australia (41) as well as European countries (3,4, 9). CD is rare in Japan (42). The incidence remains uncertain in China, with reports suggesting a possibly high incidence in the Jiangsu province of China (43).

Compared with other digestive diseases the number of researches in CD is increasing these days. For example, compared with Crohn's disease, CD researches are spread throughout the world and more dominated by expert authors (26). Given the growth in the number of CD investigation and the increased diversity of projects, gastroenterologists and other clinicians are more likely to meet CD study and this may lead to increased awareness and diagnosis rates, resulting in the improved care of CD patients.

## Malignancy in celiac disease in the Asian-Pacific Region

As stated in the introduction there is an absolute and relative lack of studies regarding malignancy associated with CD from the Asian-Pacific region. Selby et al. reported a series from a single centre in Australia, confirming a relatively high incidence of lymphoma and small bowel adenocarcinoma in patients diagnosed with CD over a 19 year period (44). Other studies have reported case studies of small bowel adenocarcinoma in patients diagnosed with CD. Rajabalinia et al. reported the case of a 43-year-old male who was presenting with complaints of intractable nausea and vomiting and diagnosed with CD in Iran (45). After several surveys, one large mass lesion was identified using push enteroscopy, in the third part of duodenum and a histopathological investigation was compatible with adenocarcinoma. Subsequently, a duodenal segment resection was performed. After surgery, and starting GFD the patient recovered well and left the hospital in good condition. The authors advised that clinicians should consider the possibility of small bowel malignancy in CD patients with distressing symptoms such as nausea and vomiting unresponsiveness to treatment (45). Series have also been reported of small lymphoma and adenocarcinoma. Other studies, from countries with a low prevalence of CD have suggested that CD is rarely associated with isolated cases of NHL and EATCL localized to the GI tract and small bowel adenocarcinoma. Makishima and colleagues reported a asymptomatic case of diffuse large B-cell lymphoma (DLBCL) associated with celiac disease in a Japan. They concluded that even though no GI symptoms were seen in patients with DLBCL, a gluten-free diet should have been strongly recommended (46). In another study in China in 2011, Sun et al. examined the clinicopathological and molecular features of 38

cases of primary intestinal T-cell and NK-cell lymphoma and showed that most cases of primary intestinal T-cell and NK-cell lymphoma are not associated with celiac disease (47). Clinical, laboratory and histological features of 52 Iranian patients with CD were evaluated in other study (48). Lymphoma in the jejunum was observed as main malignancies in two cases (male). The main complication of these two patients was bowel obstruction, and anemia. These two cases had a long history of symptoms of celiac since childhood. Jafroodi et al. report of the atopic dermatitis and Hodgkin's lymphoma in a 11-year-old boy with celiac disease (49). Under GFD all his sign and symptoms were improved but during this time a cervical lymph node was developed. The histopathologic findings were consistent with Hodgkin's disease. After 4 year's chemotherapy and also putting on GFD, the patient in complete remission for Hodgkin's disease.

On the other hands, a recent multicenter study from the Asia Lymphoma study group in South East of Asia identified 38 EATL patients within a 19-year period. Celiac disease did not a cause of any malignancy in this group of patients (50).

## Conclusion

A GFD remains the mainstay of CD treatment and the majority of clinical and serological parameters will improve after starting this diet (51, 52). There is considerable evidence that a gluten free diet is protective against the development of some types of malignancies (5, 16, 39, 40, 44, 53). Holmes et al. in 1989 suggested that adherence to a GFD for five following years will significantly decreases the rate of malignancies such as cancer of the mouth, pharynx, esophagus and lymphoma (54). Early diagnosis and adherence to a GFD may prevent the risk of developing a CD associated malignancy (5, 12).

As the correlation between CD and gastrointestinal cancer were reported in a few studies

in Asian Pacific region we suggest two points; first it is possible the prevalence of GI cancer in celiac patients in this region is very low and most of the patients diagnosed at early stage of celiac and respond to GFD very well. On the other hand may be the clinicians missed these type of patients and do not include celiac disease screening in patients referred with GI cancers. It is hoped that more studies, assessing the risk of malignancy for patients with CD, from the Asian and Pacific regions will be performed and published.

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