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ABOUT COVER

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REVIEW

Association between intestinal neoplasms and celiac disease: A review

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Abstract

Celiac disease (CD) is a chronic immune-mediated intestinal disease with genetic susceptibility. It is characterized by inflammatory damage to the small intestine after ingestion of cereals and products containing gluten protein. In recent years, the global prevalence rate of CD has been approximately 1%, and is gradually increasing. CD patients adhere to a gluten-free diet (GFD) throughout their entire life. However, it is difficult to adhere strictly to a GFD. Untreated CD may be accompanied by gastrointestinal symptoms, such as diarrhea, abdominal pain, and extraintestinal symptoms caused by secondary malnutrition. Many studies have suggested that CD is associated with intestinal tumors such as enteropathy-associated T-cell lymphoma (EATL), small bowel cancer (SBC), and colorectal cancer. In this study, we reviewed related studies published in the literature to provide a reference for the prevention and treatment of intestinal tumors in patients with CD. Compared with the general population, CD patients had a high total risk of SBC and EATL, but not colorectal cancer. The protective effect of GFD on CD-related malignancies is controversial. Further studies are needed to confirm whether GFD treatment can reduce the risk of intestinal neoplasms in CD.

Key Words: Celiac disease; Gluten-free diet; Intestinal neoplasms; Small bowel cancer; Enteropathy-associated T-cell lymphoma; Colorectal cancer

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Core Tip: Celiac disease (CD) is an autoimmune intestinal disease caused by intake of gluten-containing cereals and their products by individuals with genetic susceptibility genes. The global prevalence rate is approximately 1% and is gradually increasing. CD can lead to intestinal mucosal damage and secondary malnutrition caused by extraintestinal symptoms. In this study, the total risk of small bowel cancer and enteropathy-associated T-cell lymphoma in CD patients was higher than that in the general population, but the risk of colorectal cancer in CD patients was not significantly higher. The protective effect of a gluten-free diet on CD-related malignancies is controversial.

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INTRODUCTION

Celiac disease (CD) is a chronic immune-mediated intestinal disease characterized by permanent intolerance to glutenin. Ingestion of glutathione by CD-sensitive individuals triggers adaptive and innate immune responses, leading to intestinal inflammation[1-5]. Genetic susceptibility plays an important role in the pathogenesis of CD and is strongly associated HLA-DQ 2 and/or HLA-DQ8 haplotypes[6]. However, a small number of HLA-DQ2-negative and/or HLA-DQ8-negative individuals also develop CD, suggesting that other genetic and/or environmental factors, including the gut microbiota, may play a role in the pathogenesis of the disease[7-9]. The presence of *Helicobacter pylori* reduces the risk of developing CD[10]. Reovirus and rotavirus are also associated with CD[11,12].

According to a systematic review, the global prevalence of CD was 1.4% using serum samples and 0.7% using biopsy samples[13]. The prevalence of biopsy-confirmed CD in some populations is as high as 4.3%[14]. However, studies have shown that the worldwide incidence of CD is underestimated. A considerable number of patients have not been diagnosed or have been diagnosed late, partly because of extensive clinical manifestations. In addition to typical gastrointestinal problems, patients may have various extraintestinal symptoms or may even be asymptomatic[15-20]. Extraintestinal manifestations of the disease can affect almost any organ, including the nervous, endocrine, liver, skin, blood, reproductive, cardiovascular, and musculoskeletal systems, and are usually associated with more severe clinical and histological manifestations[21,22]. The CD diagnosis recommendations of the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) include preliminary serological screening of anti-tissue transglutaminase immunoglobulin A, anti-endomysium antibodies, and anti-deamidated gliadin peptide, and at least one biopsy obtained from the duodenal bulb)[23-30]. Characteristic small intestinal mucosal injury is the basis of diagnosis. Upper gastrointestinal endoscopy can directly reveal gross changes in the small intestinal mucosa, including scallops, villous fold reduction, cracks, mosaic patterns, and nodules[31]. However, their absence does not rule out the diagnosis of CD. Therefore, duodenal biopsies should be included to improve the diagnostic rate[32] (Figures 1 and 2). The modified Marsh–Oberhuber standard is useful for diagnosis[2,33,34].

The mortality rate in CD patients is higher than that of the general population[35-37]. An increased risk of death is mainly observed within a few years after diagnosis [38-40]. A cohort study from Scotland found a temporary increase in the risk of mortality among adults diagnosed with abdominal cancer, mainly malignant lymphoma. However, the risk of mortality declined steadily over time after diagnosis, and the risk of malignancy decreased 15 years after diagnosis[41]. However, a large epidemiological registry study in the United Kingdom found that although non-Hodgkin's lymphoma (NHL) had a high mortality of 0.15%, there was no significant increase in the risk of death in people with CD compared with the general population [42]. A recent population-based cohort study from Sweden reported increased mortality in patients with CD. Although the overall risk of death is the highest in the first year after diagnosis, it persists for 10 years after diagnosis. Cardiovascular disease, respiratory disease, and cancer are the main reasons for the increased risk of

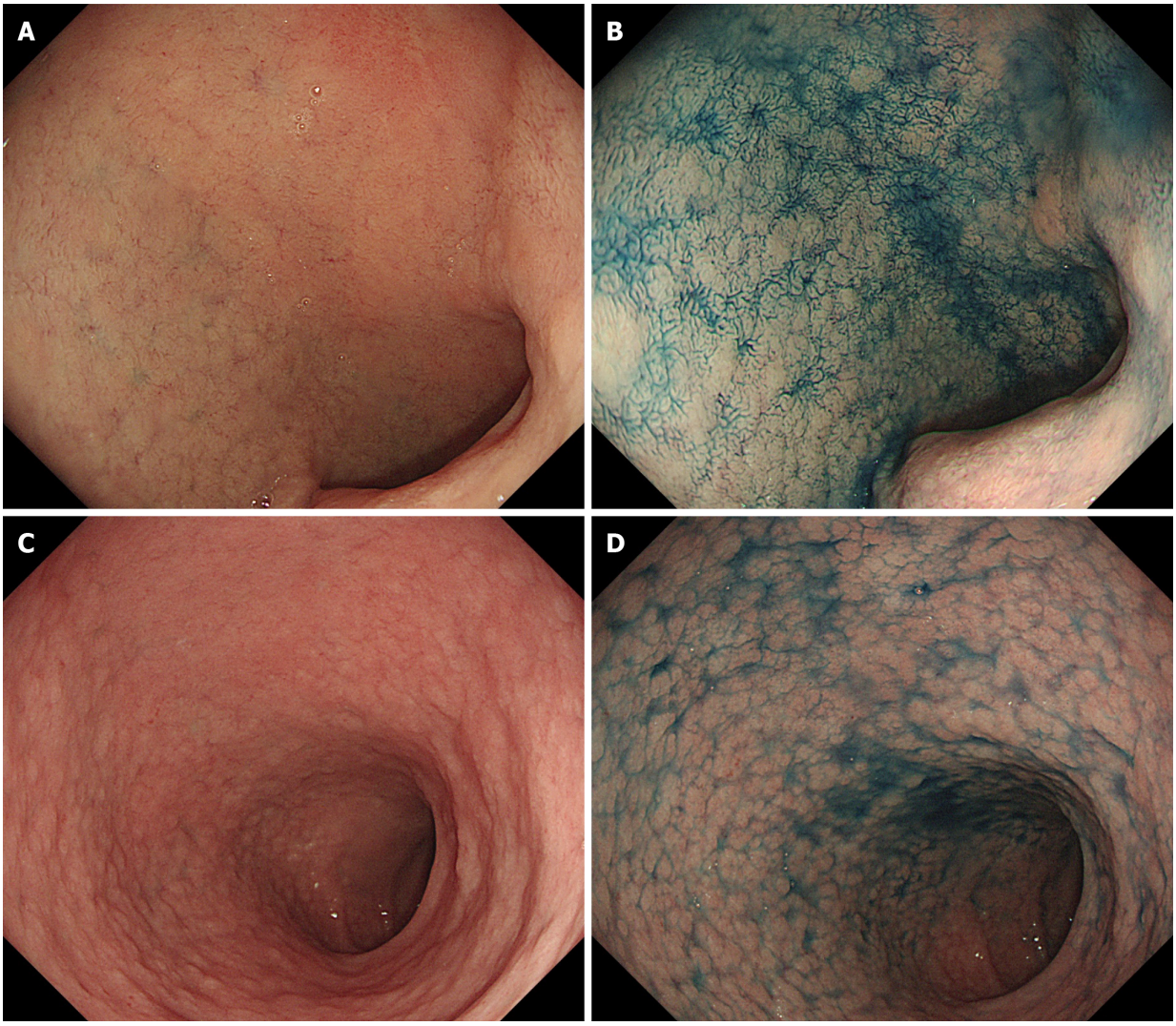

Figure 1 Endoscopic findings in patients with and without celiac disease. A: High-definition endoscopic photo of normal duodenal bulb. The villi are clearly visible, and there is no evidence of atrophy or scalloping of the folds; B: The normal duodenal bulb is stained with indigo carmine; C: High-definition endoscopic photo of celiac disease showing the characteristic loss of circular folds, fissuring, and cobblestone appearance of the duodenal mucosa; D: Duodenal bulb from a patient with celiac disease stained with indigo carmine.

death[43].

Glutenin is mainly found in wheat, barley, rye, and oats[44]. Currently, the only effective treatment for CD is a lifelong strict gluten-free diet (GFD), which usually alleviates symptoms and improves intestinal mucosal damage[45,46]. There is evidence that early adoption of a GFD can prevent CD-related complications[35,47]. However, because of the extensive use of wheat in food, gluten may be inadvertently ingested[48-50]. Low doses of glutenin in the diet of patients with CD may also be harmful[51]. In addition, despite adherence to a GFD, up to 30% of patients have persistent symptoms. In 60% of patients, the villi of the small intestine atrophy, heal poorly, and the intestinal disease may persist[45,49,52]. Poor disease control has been associated with small bowel cancer (SBC), colorectal cancer, and enteropathy-associated T-cell lymphoma (EATL)[53-55]. However, the relationship between CD, GFD, and intestinal neoplasms is controversial. The purpose of this paper was to review the existing literature on CD and intestinal tumors and discuss their correlation.

CD AND SBC

Primary SBC is a rare malignant tumor, accounting for approximately 2%–3% of all gastrointestinal carcinomas[56-58]. Studies have confirmed that compared with the population without CD, patients with CD had a significantly increased risk of small

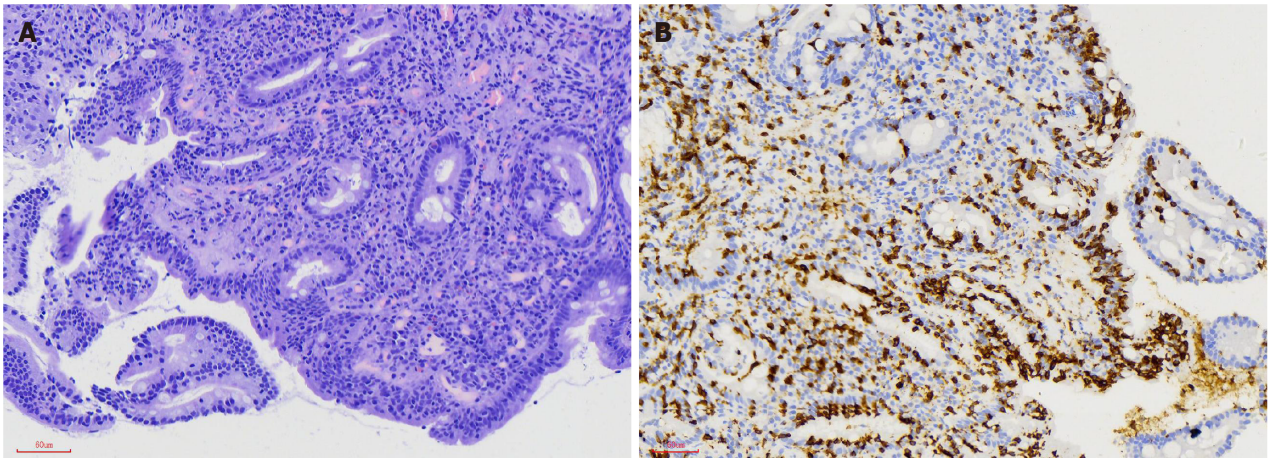

Figure 2 Histologic findings in celiac disease. A: The specimen shows total villus atrophy and increased intraepithelial lymphocytes (IELs), 60/100 epithelial cells, and crypt hyperplasia (hematoxylin and eosin; original magnification 200 ×); B: CD3 immunohistochemistry (200 ×).

intestinal adenomas and adenocarcinomas, but not carcinoids[59,60]. The risk of SBC in CD patients is 4–10 times higher than that in healthy individuals[55,61]. In a large questionnaire survey in the United States, 0.2% CD patients had SBC[62]. Compared with CD patients with nonmalignant tumors, CD patients with SBC were older[63]. SBC is also the main cause of death in young adults with early-onset CD triggered by chronic intestinal mucositis[64]. Chronic inflammation is associated with an increased risk of malignancy[65-67]. Compared with Crohn's disease-related or sporadic SBC, CD-related SBC is more prone to mismatch repair defects[68,69]. In addition, CD-related SBC often contains a large number of tumor-infiltrating lymphocytes, particularly medullary-type lymphocytes[70]. Giuffrida *et al*[71] found that CD-associated SBC was often infiltrated by programmed death 1 (PD-1)-positive T cells, and PD-L1 was expressed in tumor/immune cells in more than one-third of cases. Some studies have reported that the mucosal lesions of CD are mainly located in the proximal small intestine, especially in the ileum, and CD-mediated SBC lesions have a similar distribution[72,73]. However, one study also showed that small intestinal adenocarcinoma in CD patients was more likely to occur in the jejunum[74]. Therefore, it is necessary to further study the location of CD-related SBC lesions in the small intestine.

Early detection of CD and early initiation of a GFD may inhibit or help to prevent chronic inflammation, thereby reducing the risk of SBC. However, a GFD may also alter the intestinal microbiota, thereby affecting the risk of cancer in CD patients[75,76].The main treatments for SBC include surgical resection and adjuvant chemotherapy for positive lymph nodes. Chemotherapy is recommended for the treatment of metastasis. Palascak-Juif *et al*[77] found that if preventive surgery (mainly ileectomy) is performed after 10 years of follow-up, 70% SBC cases can be prevented. However, the need for ileectomy requires further investigation. The prognosis of small intestinal adenocarcinoma is poor because the 5-year survival rate is 39%–46%[78]. However, the survival rate for CD-associated small intestinal adenocarcinoma is significantly higher than that for small intestinal adenocarcinoma without CD[68,79].

CD AND COLORECTAL CANCER

Colorectal neoplasms mainly include colorectal polyps, adenomas, advanced lesions, and cancers. The incidence and mortality rates of colorectal cancer are the third and second highest, respectively, among those of all malignancies[80]. Colorectal polyps, including adenomatous and non-adenomatous polyps, are abnormal protrusions on the surface of the large intestine. Colorectal adenomatous polyps are considered the most important precancerous lesions that develop into colorectal cancer through the adenomatous carcinoma sequence. Therefore, early screening, early detection, and early treatment of precancerous lesions can prevent the occurrence and development of colorectal cancer[81,82]. Although the incidence of SBC is high in CD patients, the relationship between CD and colorectal cancer is controversial. In 2002, a large, national population-based cohort study showed that CD patients had an increased risk of colorectal cancer, and that the cancers mainly occurred in the ascending and

transverse colon[61]. A retrospective case-control study reported that adult patients with CD had an increased prevalence of colorectal adenomas compared with healthy controls[83]. In a population-based cohort study of patients with CD, the most common gastrointestinal cancer was colon cancer. Although the risk of colon cancer increased eight-fold during the first year of follow-up of a previous study, there was no increase in the risk after the first year of biopsy[54]. In 2014, an Italian study involving 1757 patients confirmed that CD was associated with a decreased risk of colon cancer[84]. However, in most studies, the risk of colorectal cancer in CD patients was not significantly correlated with the risk in the general population[35,85-87]. A meta-analysis conducted in 2015 found no significant association between CD and colon and rectal cancer[59]. A systematic review and meta-analysis by Lasa *et al*[88] found that there was no causal relationship between CD and colorectal adenoma. However, the incidence of colorectal cancer in patients with CD was similar to or lower than that in the general population[84]. It may be related to the increased utilization of medical care by patients with known CD, especially when gastroenterologists perform polypectomy during colonoscopy screening[81]. In addition, immune changes such as an increase in the number of intestinal intraepithelial lymphocytes (IELs) in CD patients may prevent the development of epithelial malignancies[89].

Whether GFD can reduce the risk of colon cancer in patients with CD is still inconclusive. A multicenter retrospective case-control study showed that CD was not associated with an increased risk of colorectal cancer and that adherence to a strict GFD was associated with the presence of adenoma[90]. Most studies of adults with CD have shown that a non-GFD diet does not increase the risk of colon cancer[91]. Untreated CD may have a protective effect against colon cancer because impaired absorption of fat or fat-soluble agents, including hydrocarbons and putative co-carcinogens, which are associated with the development of colon cancer. Some substances may be poorly absorbed and rapidly excreted. Further studies are required to clarify the relationship between colorectal cancer and CD.

CD AND EATL

EATL is a rare peripheral T-cell lymphoma that was first reported by O'Farrelly *et al* [92] in 1986. It is a CD-associated NHL of the upper small intestine. It is estimated that approximately 2%–3% CD patients will develop intestinal lymphoma, and EATL is currently considered the most common subtype of primary intestinal T-cell lymphoma [93,94]. There are two types of EATL. Classic EATL (type I) accounts for approximately 80%–90% of cases, and is related to CD. Type II EATL is not associated with CD. Here we mainly discuss the former. Severe complications, such as refractory celiac disease (RCD) or malignant tumors, occur in 2%–5% adult CD patients. There are two types of RCD. The phenotype of IELs is abnormal in RCD II patients and normal in RCD I patients. Approximately 50%–60% RCD II patients develop into EATL within 5 years after diagnosis[95]. Patients with EATL usually present with weight loss, anemia, abdominal pain, diarrhea, fever, and vomiting. Intestinal ulcers, stenosis, and perforation are typical manifestations of EATL. Multifocal involvement of the jejunum is the most common, followed by that of the ileum, duodenum, stomach, and colon [96].

Although the relationship between CD and EATL has been established, it is unclear whether a GFD can reduce the occurrence of EATL. Holmes *et al*[97] reported that compared with CD patients who followed a strict GFD for > 5 years, those with an unlimited or a low-gluten diet had an increased risk of intestinal NHL. One study reported that in a cohort of 335 patients who underwent early treatment for CD, 83% adhered to the GFD, and no NHL cases were found[98]. A Swedish study reported that for CD patients < 10 years of age, the risk of developing lymphoma was moderate and did not significantly increase[61]. A population-based prospective study in 1757 CD patients performed by Silano *et al*[99] found that a strict GFD had a protective effect on the development of EATL. In contrast, a retrospective study from the United Kingdom found that patients with good histological responses to a GFD did not have a reduced risk for intestinal lymphoma[100]. Green *et al*[101] reported the occurrence of intestinal NHL in patients with CD after years of following a GFD. The differences in the conclusions of these studies might be explained by a number of reasons. First, the relatively short dietary duration observed may not be sufficient to reverse the effects of years of gluten exposure[102]. Second, it is very difficult to comply with a strict GFD because of the small amount of gluten present in non-cereal foods[103]. Third, there is no non-invasive method to determine compliance with a GFD[104].

RCD II is characterized by the presence of a large number of abnormal clonal T cells, which are associated with poor prognosis. Because of the risk of conversion to EATL, RCD II is referred to as prelymphoma or low-grade lymphoma, with a high mortality rate. The 5-year survival rate of patients with RCD II is as high as 58%[50]. If EATL occurs, the 5-year survival rate is reduced to 8%. Fewer than 14% patients with RCD I develop EATL within 5 years of diagnosis[105]. The risk factors of EATL include older onset age, male sex, HLA-DQ2 homozygous, ulcerative jejunitis, and/or the presence of abnormal T cells[105,106]. The poor prognosis of EATL is associated with a large tumor volume and elevated levels of C-reactive protein and lactate dehydrogenase[94,107,108]. A comprehensive examination can improve the accuracy of EATL detection. For patients with suspected EATL, comprehensive evaluation, double-balloon enteroscopy biopsy, video capsule enteroscopy, magnetic resonance enteric examination, and ^{18}F- fluorodeoxyglucose positron-emission tomography-computed tomography can be used for confirmation[95].

There is essentially no difference in the treatment of lymphoma in patients with and without CD. Surgery, radiotherapy, and chemotherapy are commonly used. For patients diagnosed early, the treatment effect is better[109]. Patients with RCD I generally respond well to corticosteroids and immunosuppressive drugs such as thiopurine and infliximab. However, patients with RCD II do not respond well to those drugs[50]. The key goal of RCD II therapy is to destroy the precancerous clonal T-cell population. Chemotherapy (*e.g.*, with the purine analogue cladribine) and autologous stem cell transplantation (ASCT) have been used, and their success rates in patients with RCD II vary[110]. The cyclophosphamide, doxorubicin, vincristine, prednisone scheme is widely used, however, previous studies have shown that the overall median survival time was only 7 mo[111-113]. In a small case series, the combination of ifosfamide, etoposide, epirubicin/methotrexate-ASCT increased the 5-year survival rate to 60% compared with the anthracycline based chemotherapy[114]. CD disrupts cell-level regulation, leading to overexpression of IL-15 and chronic intestinal inflammation, which in turn leads to the proliferation of IELs. Recent developments include Janus kinase inhibitors that can block IL-15 and reduce IELs, which has been confirmed in animal models. Biologic drugs provide a new possible method for the treatment of RCD and EATL[115-118].

CONCLUSION

The available data show that the total risk of SBC and EATL, but not colorectal cancer, in CD patients is higher than that in the general population. The protective effect of a GFD on CD-related intestinal neoplasms is controversial. It is necessary to conduct more studies, especially prospective cohort and experimental studies, to further evaluate whether GFD treatment can reduce the risk for intestinal malignancies in patients with CD and explore the associated risk factors and biological relationships that may lead to CD-related intestinal malignancies.

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