

Colorectal Cancer in Biopsy-defined Celiac Disease Seen over 30 Years: Rare, Even in Elderly Adults

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Abstract Some malignant disorders, including colorectal cancer (CRC), may be reduced in celiac disease. In this study, 154 older adults, including elderly adults over age 60 years, were seen over 30 years. All patients were biopsy-defined and treated with a gluten-free diet. A single elderly female had an early stage colon cancer in the cecum but a persistent iron deficiency anemia led to later detection of biopsy-defined celiac disease and a gluten-free diet mucosal response. This study indicates that colon cancer is rare in biopsy-defined celiac disease. In this study, there were no gastric, pancreatic or hepato-biliary tract cancers seen. Genetic and environmental dietary factors may play a role, however, the rarity of colorectal cancer in other celiac-associated colonic diseases (eg., collagenous or lymphocytic colitis) suggests that an immune-mediated protective effect may occur.

Keywords: colorectal cancer, celiac disease, cancer prevention, elderly celiac disease

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1. Introduction

Colorectal cancer (CRC) is a major cause of cancer-associated morbidity and mortality in North America and Europe. In particular, prior studies have estimated that CRC is the fourth most commonly diagnosed internal cancer (exceeded by breast, prostate and lung) and contributes about 10% of new cancer cases in both men and women each year. It has been estimated that approximately 6% of the American population will develop an invasive CRC. Much investigative energy has been directed towards diseases that may predispose to development of CRC. Others have increasingly focused on screening and early detection of CRC because there is a marked increase in survival for early disease compared to later diagnosis at an advanced stage [1,2].

Some chronic inflammatory intestinal diseases, such as Crohn's disease, particularly with colon involvement, and ulcerative colitis, have been associated with increased development of CRC, possibly related to the duration and length of colonic involvement with the inflammatory process. However, this has rarely been defined in other immune-mediated colonic diseases (i.e., collagenous colitis, lymphocytic colitis) [3,4,5,6,7], or indeed, other chronic and long-standing gastrointestinal diseases, such as celiac disease, that has also been linked in a prospective evaluation to collagenous [8] and other microscopic forms of colitis [9,10]. In the present study, patients from a single clinician database of biopsy-defined celiac disease

over more than 30 years were retrospectively reviewed for cases of CRC.

2. Patients and Methods

Clinical office, hospital and medication records from biopsy-defined celiac disease patients in the database were reviewed, based on previously published diagnostic criteria [11,12]. Only records from older adults (> 30 years of age) and elderly adults (> age 60 years) at the time of initial diagnosis of celiac disease were included. All patients in this study were symptomatic initially referred for evaluation of symptoms, including abdominal pain, diarrhea and/or weight loss. Asymptomatic patients, discovered with serological screening were not included. Endoscopic duodenal biopsies from multiple sites were obtained after an overnight fast and, in most patients, intravenous sedation and topical xylocaine spray were provided before the procedure. Routine biopsy processing was done with specimens obtained with regular pinch forceps and placed in fixative after orientation on mesh or filter paper with "the mucosal surface up" in the endoscopy suite. Routine histopathological processing through the biopsy core was performed as previously noted [13] and interpreted by experienced endoscopic biopsy pathologists. All biopsies were also independently reviewed by the author investigator as a second trained observer of mucosal biopsy material [13].

In this study, only patients with an initial severe "flat" biopsy lesion (i.e., crypt hyperplastic villous atrophy,

Marsh 3) with intraepithelial lymphocytosis were included in this long-term evaluation, as noted elsewhere [14], characteristic of celiac disease. Patients with minimal architectural disturbance or epithelial lymphocytosis alone in the initial biopsies were not included because North American studies involving both children and adults have suggested that most patients with this limited severity of histopathological change do not have celiac disease [15,16].

All patients were reviewed and monitored by the clinician investigator and a specially-trained dietitian. Treatment was solely with a gluten-free diet. Dietary compliance was defined by ongoing clinical evaluation and subsequent biopsy evaluation as previously described to define mucosal recovery and mucosal healing [14]. Some patients were referred from other gastroenterologists, or developed a related or complicating illness, including collagenous sprue or malignant lymphoma, or received corticosteroids or immunosuppressant medications. These patients were either not available for further follow-up or prohibited from further biopsy studies.

Further imaging studies were done by colonoscopy, sometimes following barium contrast studies (prior to 2000) or other imaging modalities with CT/MRI, sometimes with contrast. In most patients, colorectal biopsies were also done to exclude microscopic forms of colitis, often associated with celiac disease [9,10], as well as the ileum. As previously reported [17], biopsies from the ileum in 1 patient being investigated for diarrhea and weight loss showed epithelial lymphocytosis without significant architectural change that led to duodenal biopsies showing characteristic features of celiac disease.

2.1. Study Population

A total of 154 patients (55 males, 99 females) with severe “flat” biopsy changes accompanied by epithelial lymphocytosis (Marsh 3) were included in this long-term evaluation. This patient population was extracted from a larger cohort of 182 patients, detailed elsewhere [14] that also included 28 younger patients (5 males and 23 females) from ages 15 to 30 years. Age ranges for the study population here at the initial biopsy are noted in Table 1. The number of females were the same or exceeded the number of males in each age group. In this study, the total patient population was approximately equally distributed between 3 groups (i.e., 30-45 years, 46-60 years, as well as an elderly adult population over age 60 years) at the time of the initial diagnosis. Increased initial recognition of adult celiac disease in the elderly has been described [18] and previously reviewed [19]. As previously noted [14] in this population, mucosal recovery and healing of the small intestinal mucosa was lowest in this elderly population compared to other age groups under age 60 years, including females, and, particularly, males. In this population, over 85% also had histologically-documented mucosal recovery and healing with repeated biopsies [14], sometimes not accomplished even after 2 years on a prescribed gluten-free diet, or never accomplished (i.e., total about 15%). In some of these patients with persistent inflammatory change, other disorders occurred. In males, there were 6 with malignancies including an early stage small intestinal adenocarcinoma or lymphoma. In females, 2 also developed lymphoma.

Table 1. Ages of Males and Females*

	31-45 years	45-60 years	61-80+ years
Males	15 (27.3)	24 (42.4)	16 (37.0)
Females	42 (43.6)	24 (24.2)	33 (33.3)
Total	57 (37.0)	48 (31.2)	49 (31.8)

*Total study population (n=154) with severe “flat” biopsy changes (i.e., crypt hyper- plastic villus atrophy, Marsh 3) included 55 males and 99 females. Numbers in parentheses, calculated percentages. Modified from Reference 14.

2.2. Colon Cancer

In this evaluation of 154 patients over the age of 30 years, only a single colon cancer was found (about 0.64% of patients) in a retired female physician, age 69 years.

She reported a family history of CRC and had a normal screening colonoscopy in 2002. In 2007, an iron deficiency anemia developed leading to another colonoscopy and detection of an early stage cecal cancer. A right hemicolectomy was done and lymph node evaluation (20) was negative. Because of a persistent iron deficiency anemia over the next year, further investigations, including repeated colonoscopy, revealed positive serological studies (tissue transglutaminase antibodies, over 145 units; normal, < 20 units) and endoscopic small bowel biopsies (showing crypt hyperplastic villus atrophy and epithelial lymphocytosis). A gluten-free diet was initiated with resolution of her abnormal tissue transglutaminase level. Later biopsies of her small bowel and resected colon were normal. In addition, 2 family members were later diagnosed with celiac disease, but no other family member with CRC was detected later. Finally, none of the other 153 patients (including males or females) in this cohort developed CRC.

3. Discussion

This study evaluated a very selected population of older adults seen over 30 years with biopsy-defined celiac disease, including a significant number classified as elderly adults, initially diagnosed over age of 60 years. Only a single celiac patient in this cohort had CRC, and in this instance, celiac disease was only discovered later during added investigations for persistent iron deficiency anemia. Given the reported percentage of the American population with CRC, less than 1% represents a substantial reduction in this celiac cohort. Ordinarily, CRC is detected in older adults with advanced age, particularly over age 60, even though CRC may occasionally occur in younger adults. Prior population cohort and case studies in celiac disease have also noted a low incidence of CRC [21,22,23,24], however, in the present study, younger patients with celiac disease were excluded as CRC in this age group would be expected to be even more limited. Stated differently, if these younger adults were included, the actual percentage of patients with CRC in the entire group of biopsy-defined celiacs would have been even lower. This study further confirms an earlier study that noted an absence of CRC in celiac patients [25] even though some, particularly elderly patients referred from other gastroenterologists, were excluded here because of inadequate on-site follow-up, complicating disease or added drug treatments for celiac

disease (i.e., steroids and immunosuppressants). Although not specifically evaluated here, no patient in this series of biopsy-defined celiacs developed gastric, pancreatic or hepatobiliary tract cancer suggesting that celiac disease may be protective against multiple malignancies.

An important issue raised by the results here is the mechanism for this protective role of celiac disease for some malignant diseases, particularly CRC. A single case of CRC in this series, that included elderly patients, was observed over a period of approximately 30 years in this clinical investigative experience. This is consistent with other reported descriptive series [21,22,23,24,25], but, perhaps, has been under-emphasized. While genetic factors may play a role, other extrinsic or environmental factors may also be important. For example, dietary fat or fat-soluble agents, including hydrocarbons or other putative co-carcinogens, implicated in development of colon cancer and other gastrointestinal malignancies, may be poorly absorbed or rapidly excreted. The intestinal microbiome may also be substantially altered in celiac disease leading to alterations in luminal "conditioning" with changes in luminal metabolism and disposition of nutrients, including carcinogens [26,27,28]. These observational findings here in celiac disease suggest that future studies are needed to further explore their potential pathogenetic implications for CRC.

Also intriguing is the potential role of the immune system in celiac disease. At least a portion of the small intestinal mucosal pathology in celiac disease includes a marked increase in the number of intra-epithelial lymphocytes. In some with celiac disease, this finding may also be observed in the colorectal mucosa. Reports in disorders with increased intra-epithelial lymphocytes (eg., collagenous and lymphocytic colitis) later developing CRC are impressively rare, even in patients with long-standing disease [3,4,5,6]. Even more intriguing is the detection of latent lymphocytic enterocolitis with celiac disease after resection of colon cancer [7]. Possibly, these immunological changes play an important and critical protective role in celiac disease for colonic diseases, such as CRC. Further study of these complex interactions between the immunological changes noted in celiac disease and diseases, including CRC, are needed.

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