Adult Celiac Disease and Its Malignant Complications

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Adult celiac disease is a chronic intestinal disorder that has been estimated to affect up to 1-2% of the population in some nations. Awareness of the disease has increased, but still it remains markedly underdiagnosed. Celiac disease is a pathologically defined condition with several characteristic clinical scenarios that should lead the clinician to suspect its presence. Critical to diagnosis is a documented responsiveness to a gluten-free diet. After diagnosis and treatment, symptoms and biopsy-proven changes may recur and appear refractory to a gluten-free diet. Recurrent symptoms are most often due to poor diet compliance, a ubiquitous and unrecognized gluten source, an initially incorrect diagnosis, or an associated disease or complication of celiac disease. Some patients with persistent symptoms and biopsy-proven changes may not have celiac disease at all, instead suffering from a sprue-like intestinal disease, so-called unclassified sprue, which is a specific entity that does not appear to respond to a gluten-free diet. Some of these patients eventually prove to have an underlying malignant cause, particularly lymphoma. The risk of developing lymphoma and other malignancies is increased in celiac disease, especially if initially diagnosed in the elderly, or late in the clinical course of the disease. However, recent studies suggest that the risk of gastric and colon cancer is low. This has led to the hypothesis that untreated celiac disease may be protective, possibly due to impaired absorption and more rapid excretion of fat or fat-soluble agents, including hydrocarbons and other putative cocarcinogens, which are implicated in the pathogenesis of colorectal cancer. (Gut and Liver 2009;3:237-246)

**Key Words:** Adult celiac disease; Malignancy in celiac disease; Lymphoma; Small intestinal cancer; Colonic neoplasms

INTRODUCTION

Celiac disease has become increasingly recognized. In Finland, a prevalence of up to 2% has been noted in recent decades. In adults, the disorder often presents with chronic diarrhea, weight loss and malabsorption. However, some have no diarrhea and weight loss is not evident. Instead, iron deficiency or alterations in blood chemistry values (e.g., low serum albumin) occur. Or, a closely-linked clinical disorder may be present (e.g., autoimmune thyroid disease, insulin-dependent diabetes, dermatitis herpetiformis). More recently, there has been an increased recognition that some neurological disorders, such as dementia in the elderly, should even be considered. Finally, positive screening blood tests (e.g., endomysial or tissue transglutaminase antibodies), though not diagnostic, may lead to suspicion of celiac disease.

DIAGNOSIS OF CLASSICAL CELIAC DISEASE

Diagnosis of celiac disease rests on 2 specific, and sequential, criteria: first, typical biopsy changes need to be shown in proximal small intestine before treatment; and second, an unequivocal clinical and/or pathological response must be documented in response to a gluten-free diet. With a gluten-free diet, the diarrhea should resolve and weight gain should occur, at least sufficient to provide a convincing clinical diagnosis. However, with limited symptoms, repeated biopsies may be needed to demonstrate histological improvement. Recently, it has become appreciated that over 50% of celiacs may now be classified as overweight or obese. In these, weight gain has also been shown with a gluten-free diet. Serologic tests may be used for screening, but cannot
be solely relied upon for diagnosis.\textsuperscript{5,6} Interestingly, the fate of different celiac antibodies in genetically at-risk children on a normal diet have been examined and shown to spontaneously disappear.\textsuperscript{7} False negative serological tests also occur (e.g., concomitant IgA deficiency). So, if there is clinical suspicion of celiac disease in an adult, then a biopsy should be done. Clearly, a biopsy will be needed to determine if the serologically-based suspicion of celiac disease was correct since false-positive blood tests also occur. In a recent study, for instance, no biopsy evidence of celiac disease was present despite very high tissue transglutaminase values.\textsuperscript{8}

Histopathological changes in classic celiac disease are typically present in the proximal rather than distal small bowel and have been classified elsewhere based on the degree of altered architecture.\textsuperscript{3} Other different classification methods have been reported. For example, the Marsh classification\textsuperscript{9} as modified by Oberhuber et al.\textsuperscript{10} has found its way into the clinical realm, but a recent histopathological evaluation concluded that this particular schema was cumbersome and intraobserver agreement was reduced.\textsuperscript{11}

Most often, a “severe (flat) mucosal lesion” is found (Figs. 1 and 2). This has also been labeled the “flat destructive” or “Marsh 3 lesion”. The villi are rudimentary. Lamina propria lymphoid cell elements are increased, particularly plasma cells and lymphocytes. Intraepithelial lymphocytes are also increased. The surface epithelium may appear more cuboidal (rather than columnar). Crypt epithelium is hyperplastic with increased numbers of cells and an increased mitotic index. Subcellular changes (e.g., increased epithelial vacuolization) occur and the glyco- calyx is altered (i.e., shown with fluorescein-linked lectins).\textsuperscript{12} With a strict gluten-free diet, these histopathological changes revert to normal.\textsuperscript{3} Comparable biopsy sites will eventually improve towards normal (Fig. 3), but these changes may require prolonged periods,\textsuperscript{13} especially in older adults.\textsuperscript{14}

In some, less severe architectural changes have been noted. In part, this may reflect increased use of serological detection methods. The villous architecture may be minimally altered and labeled a “mild lesion” (i.e., “infiltrative” or “Marsh 1 lesion”). However, epithelial cells show some loss of polarity and intraepithelial lymphocytes are increased.\textsuperscript{3,9} In a “moderate lesion” (i.e., “infiltrative hyperplastic” or “Marsh 2 lesion”), definite changes in the architecture of the villus are visualized. Less severe changes may also occur in dermatitis herpeti-
formis and asymptomatic first-degree relatives. If less severe changes are detected, however, studies to exclude other non-celiac causes, particularly infections (e.g., giardiasis, cryptosporidiosis) are critical. Epithelial lymphocytosis alone with normal small bowel architecture may respond to a gluten-free diet in about 10%, suggesting that, occasionally, an increased intraepithelial lymphocyte count alone may suggest celiac disease. Some have claimed that the celiac disease can be defined without quantitative changes in lymphocyte numbers using immunohistochemical markers alone. However, these reported qualitative changes need to be confirmed.

Pathological changes in celiac disease also occur along the length of the small bowel but may be poorly appreciated. These may have particular importance in assessing the response to a gluten-free diet. The extent of these histological changes generally seems to correlate with the severity of the clinical presentation. In classical celiac disease with diarrhea and weight loss, severe pathological changes may extend well into the jejunum. In the ileum, variably severe, often patchy, changes may also occur, but usually, ileal biopsies are normal. Some believe that this “proximal-to-distal” gradient in severity of pathological changes reflects higher concentrations of dietary gluten (or its derivative peptides) in the proximal small bowel. Alternatively, changes may be “indirect” due to immune-mediated effects driven by re-circulating memory T-cells. Even though the ileum is often normal, prior studies have shown that the ileum in celiac disease is very sensitive to gluten peptides infused through long intestinal tubes. With extensive small intestinal involvement, diarrhea and malabsorption of many nutrients may result. In contrast, deficits may be very limited if the extent of pathological change is limited (e.g., duodenum alone). In this setting, diarrhea and weight loss may not be evident. In some, only isolated iron deficiency may be present, in part, due to the major localization of celiac disease in the duodenum, the principal site for iron absorption.

Treatment with a strict gluten-free diet normally should result in resolution of the diarrhea and significant weight gain. As the clinical state improves, biopsies normalize, initially in more distal sites of small bowel involvement, and later, in the proximal small bowel. To verify that a gluten-free diet biopsy response has occurred, however, prolonged periods of gluten restriction may be necessary, even months or years, before normal proximal duodenal mucosa can be defined. Repeated endoscopic biopsies may sometimes be done, usually from duodenum. If normalization of duodenal biopsies fails to occur within a few months, a potential clinical pitfall may result. The disease may be erroneously labeled “refractory”, even though a diet-induced response may have been initiated, but only in more distally involved small bowel.

OCCULT AND LATENT CELIAC DISEASE

Celiac disease may be clinically occult and may not be detected even until late adult years. In some with subclinical disease, only isolated deficiencies of specific nutrients (i.e., iron, calcium) may develop without diarrhea or weight loss. Typical intestinal symptoms are absent or minimal and some have termed this presentation as “silent”. Some initially present with the skin disorder, dermatitis herpetiformis, autoimmune thyroid disease, insulin-dependent diabetes, a small intestinal carcinoma, or lymphoma. Occult celiac disease has also been associated with other intestinal disorders including: collagenous colitis, lymphocytic colitis, lymphocytic sclerosing cholangitis, collagenous and lymphocytic gastritis.

Latent celiac disease is a separate form of subclinical disease initially reported in dermatitis herpetiformis, and later in small intestinal lymphoma. In these reports, the small intestine was initially biopsy-normal. Then, pathological changes of variable severity were induced with a high-gluten diet showing that the mucosa was gluten-sensitive (as volunteers fed high gluten diets do not develop histological changes). These gluten-induced changes also improved in both reports with a gluten-free diet.

ROLE OF ENDOSCOPY IN DIAGNOSIS

The diagnosis of celiac disease is pathologically-based. Detection is optimized by submission of quality biopsies and close communication with an expert histopathologist. Endoscopic changes represent macroscopic changes only, are not specific and reflect the disappearance of normal mucosal patterns. These cannot be relied upon for a precise diagnosis. A smooth tubular surface with loss of normal folds, “scalloped folds”, a mucosal “mosaic” pattern with bulbar micronodularity are descriptive changes that are often used. “Scalloped folds”, however, have also been reported in Crohn’s disease with duodenal involvement. Similar macroscopic changes have been reported with emerging methodologies including capsule and double-balloon enteroscopy. These mucosal changes that occur with direct visualization, however, may be limited and their correlation with microscopic alterations is limited. Conversely, and most important, a “normal” endoscopic appearance is not sufficient to exclude celiac disease. Experienced endoscopists, for example, estimated that
Table 1. Causes of a Severe “Flat” or Variously Severe Biopsy Lesion*

| Disease                                                                 | Treatment                                      |
|------------------------------------------------------------------------|-----------------------------------------------|
| **Sprue syndromes**                                                    |                                               |
| Celiac disease (gluten sensitive enteropathy, celiac sprue)            | Gluten-free diet                              |
| Includes classic, occult and latent celiac disease                     |                                               |
| Refractory sprue (or refractory celiac disease)                        | Temporary response to gluten-free diet        |
| Collagenous sprue                                                      | Unknown                                       |
| Mesenteric lymph node cavitation syndrome                               | Unknown                                       |
| Other protein injury (soy protein, milk, oats, other proteins)         | Removal of specific protein                    |
| Unclassified sprue (or “sprue-like” intestinal disease)                | No response to gluten-free diet               |
| **Infectious causes**                                                  |                                               |
| Infectious gastroenteritis (usually in childhood)                      | Spontaneous resolution                        |
| Infections (parasites, viral, fungal, mycobacterial)                   | Treat infection                               |
| Tropical sprue                                                        | Antibiotics and folic acid                    |
| Stasis syndrome (contaminated small bowel syndrome)                    | Antibiotics                                   |
| Whipple’s disease (?Tropheryma whipplei)                               | Antibiotics                                   |
| **Deficiency syndromes**                                               |                                               |
| Nutrient deficiency syndromes                                          | Replace specific nutrient                      |
| Includes zinc, vitamin B12, folic acid deficiencies                    |                                               |
| Kwashiorkor                                                             | Adequate dietary protein                      |
| Immunodeficiency syndromes                                             | Not known                                     |
| Includes common variable immunodeficiency, AIDS                        |                                               |
| Intestinal lymphangiectasia                                            |                                               |
| **Others**                                                             |                                               |
| Crohn’s disease                                                        | Not known                                     |
| Graft-versus-host disease                                              | Graft rejection therapy                       |
| Immunoproliferative diseases (e.g., lymphoma, T- or B-cell types)      | Often chemotherapy                            |
| Macroglobulinemia or amyloidosis                                        | Often chemotherapy                            |
| Zollinger-Ellison syndrome (with acid hypersecretion)                  | Antisecretory therapy                         |

*Modified from Freeman HJ. Small intestinal mucosal biopsy for investigation of diarrhea and malabsorption in adults. Gastrointest Endosc Clin N Am 2000;10:739-53, vii.
negative. Parasites can also cause severe biopsy changes, but many can be morphologically identified in the biopsy material (e.g., Strongyloides stercoralis, hookworm, Schistosoma or Capillaria species). Some viral agents (e.g., cytomegalovirus) may be seen in the small bowel, often in the setting of an immune compromised state.43 Other disorders may cause diarrhea and/or malabsorption with severe biopsy changes like celiac disease. In some, distinct features are evident: lymphangiectasia, macroglobulinemia, amyloidosis, abetalipo-proteinemia, lipid storage disorders, radiation injury, and drugs (e.g., neomycin, busulfan, methotrexate, sulindac, azathioprine).44 Although Crohn’s disease may cause mucosal granulomas in the duodenum,45 severe architectural changes without granulomas similar to untreated celiac disease may occur in the proximal small intestine.46 In Crohn’s disease, however, these pathological findings do not improve with a gluten-free diet.

REFRACTORY DISEASE AND SPRUE-LIKE INTESTINAL DISEASE

In celiac disease, diarrhea or malabsorption may recur. Even though the mucosa may normalize with gluten restriction, severe pathologic changes may then later recur.19 A list of specific entities should be considered by the clinician (Table 2). Most often, symptoms and recurrent biopsy changes are due to poor compliance to the gluten-free diet; sometimes, this is completely inadvertent since gluten is ubiquitous and may be found in various ingested items, such as pill capsules or communion wafers. There may also be a difference in tolerance to gluten with a minimum threshold in some groups. A superimposed cause (e.g., infection) or superimposed deficiency of one or more nutrients (e.g., folic acid, zinc) may be critical in causing independent histological changes that are difficult to differentiate from changes of celiac disease. In long-standing celiac disease, pancreatic exocrine insufficiency may also occur, especially if concomitant malnutrition is evident.13 In some, it is also possible that the original diagnosis was not correct and some other cause for the severe biopsy changes was present. Finally, another related disorder (e.g., collagenous colitis) or a particularly sinister complication (e.g., lymphoma) may cause recurrent symptoms.

Rarely, an uncommon disorder, collagenous sprue, may complicate adult celiac disease.47 Sometimes, it may be appear during the investigation of malabsorption or a diarrhea disorder, without any evidence of pre-existent celiac disease. Panmalabsorption with diarrhea, weight loss, electrolyte abnormalities and marked nutritional disturbance may be seen. Small bowel biopsies reveal a pathologically distinctive sub-epithelial band of collagen. Long term nutritional support with parenteral nutrition may be needed for survival. Antibodies to endomysium in collagenous sprue may reflect an immunological link to celiac disease.48 Rarely, lymphoma may supervene in collagenous sprue.49,50 Occasionally, another distinctive syndrome may complicate celiac disease with recurrent small bowel changes of variable severity, splenic hypofunction, and mesenteric lymph node cavitatin.51 In this disorder, lymphoma has also been recorded.52

Sprue-like intestinal disease (or unclassified sprue) refers to a severe (“flat”) or variably severe (moderate to mild) mucosal lesion that has never responded to a gluten-free diet.19 Although some have labeled this entity as “refractory celiac disease”, response to a gluten-free diet has not been shown and so cannot be truly labeled with “celiac disease”. Usually, additional biopsies are abnormal despite a gluten-free diet. Most remain symptomatic and fail to clinically respond to a gluten-free diet. In some dietary compliance may be difficult to prove and histological improvement may be difficult to document, especially with duodenal biopsies alone. This group likely represents a heterogeneous collection of small bowel disorders, a “wastebasket group” with no defined cause. Some may have a “resistant form” of celiac disease, while others prove to have a “difficult-to-diagnose” lymphoma. In some, an abnormal subset of intraepithelial lymphocytes with morphologically normal, but phenotypically ab-

| Table 2. Causes of Refractory or Recurrent Disease* |
|---------------------------------------------------|
| 1. Poor compliance to a gluten-free diet (i.e., most common cause, intentional or unrecognized) |
| 2. Ubiquitous source of ingested gluten (e.g., pill capsules, communion wafers) |
| 3. Superimposed cause (e.g., folic acid deficiency, zinc deficiency) |
| 4. Second cause for symptoms (e.g., associated pancreatic exocrine insufficiency, superimposed infectious diarrhea) |
| 5. Wrong initial diagnosis (e.g., Crohn’s disease of the duodenum, “sprue-like” intestinal disease or unclassified sprue*) |
| 6. Associated or complicating clinical disorder (e.g., collagenous colitis, lymphoma) |

*Failure to initially respond to a gluten-free diet suggests “sprue-like” intestinal disease or unclassified sprue, not refractory celiac disease.
normal lymphocytes was reported. These intriguing findings could provide a prognostic marker for later lymphoma development but added confirmatory studies are needed.

**INTESTINAL MALIGNANCIES AND RISK IN CELIAC DISEASE**

Intestinal malignancies occur during the clinical course of adult celiac disease. Often, these are lymphomas that complicate already well established celiac disease. But, in some, lymphoma as well as other malignancies, such as small bowel adenocarcinoma, actually precede recognition of celiac disease, providing further evidence for an intimate clinical linkage.

The precise risk of malignancy, particularly lymphoma, in adult celiac disease has been difficult to determine because there are many confounding variables. In adults with severe biopsy changes in proximal small intestine, the overall lymphoma risk was about 8 to 10% in a tertiary care setting. Age at the time of the initial diagnosis of celiac disease seems to be a critical risk factor. If celiac disease was first diagnosed later in life, lymphoma was detected more often than if the diagnosis of celiac disease was defined earlier. Duration on the gluten-free diet may be important. Interestingly, a long-term cohort study of 285 children with celiac disease treated with a gluten-free diet described only a single small bowel lymphoma. Recent reports have also suggested that this excess lymphoma risk in celiac disease has actually decreased, related possibly to use of serological screening tests for celiac disease in those with limited symptoms.

**LYMPHOMA DIAGNOSIS IN CELIAC DISEASE**

The diagnosis of lymphoma in celiac disease may be challenging and sometimes presentations may be dramatic because most lymphomas in celiac disease occur in small intestine. Usually, these occur in jejunum, but localization in the ileum, also occurs. Duodenal lymphoma may develop while associated gastric and colonic lymphomas have been reported. Ulcerating or stenosing and obstructing tumors are often seen. Occasionally, however, the lymphoma may be multifocal or diffuse with only mucosal localization. Concomitant nodal involvement may be present. In some, a definite pathological diagnosis of lymphoma may be particularly difficult in the presence of either small intestinal (including duodenal) erosions or ulcers. Crohn’s ulceration or a label of “ulcerative jejunoileitis” may be recorded. Some of these ulcerating lesions, however, later prove to contain frankly neoplastic lymphoma cells that may be difficult to appreciate in severely inflamed small intestine. Free perforation of the small intestine may be due to lymphoma, especially if celiac disease is known to be present or suspected. Even if there is a high degree of suspicion, lymphoma may still be notoriously difficult to diagnose, despite multiple endoscopic “pinch” or suction small intestinal biopsies. In some that eventually prove to have a lymphoma, full thickness small intestinal biopsies may not have provided a definitive pathological diagnosis, especially if only focal mucosal lymphomatous involvement was present. In recent years, tissue evaluated by flow cytometry and immunohistochemical studies or PCR have been added to the armamentarium of tools to facilitate diagnosis.

**LYMPHOMA TYPES IN CELIAC DISEASE**

Lymphomas may be classified based on pathological and immunophenotypical features. Both B-cell and T-cell lymphomas occur in celiac disease. However, detection of a T-cell type more often leads to clinical suspicion of possible adult celiac disease. Primary intestinal T-cell lymphoma is recognized under the WHO classification system as enteropathy-associated T-cell lymphoma (ETL or EATL). They are very uncommon and represent an estimated 5% of all gastrointestinal lymphomas. Indeed, in a recent population-based study from the Netherlands, the disease was most common in the proximal small intestine, usually defined by surgical resection, more prevalent in males than females and rare with a reported incidence of 0.1 per 100,000 inhabitants per year. Previsously, these lymphomas were thought to be histiocytic in origin (and labeled malignant histiocytosis), but their origin now appears to be primarily from T-cells, particularly intraepithelial lymphocytes. In celiac disease (without lymphoma), intraepithelial lymphocytes express the following antigens (among others): CD3 surface + and CD 8+. In a subset of patients that seem clinically refractory to a gluten-free diet, intraepithelial lymphocytes have a different form of T-cell phenotypic expression: CD 3 shows intracytoplasmic (i.e., not surface) expression while CD 8 expression may be absent. Some studies have suggested that this may reflect a specific form of refractory disease (type 2) with a poor prognosis and a possible precursor lesion for development of lymphoma. Defective synthesis of the T-cell receptor chains appears to be responsible for the loss of surface T-cell expression.

Intestinal T-cell lymphomas are also a heterogeneous group. For example, a natural killer-like T-cell lymphoma
of the intestine may occur that appears to have a distinct immunophenotype. This entity is not known to be associated with celiac disease, progresses rapidly and has a poor prognosis.\textsuperscript{70,71} Also, cases with both B-cell and T-cell type lymphomas have been described in the single individuals with celiac disease.\textsuperscript{72,73}

Even lymphomas with T-cell immunophenotypic features have been defined in extra-intestinal sites complicating celiac disease but without lymphomatous intestinal involvement. These are rare and include hepatosplenic type T-cell lymphoma\textsuperscript{74} or lymphoma occurring in other embryologically-related or gut-derived sites, including the thyroid gland\textsuperscript{75} or bronchopulmonary and pleural sites.

Recent studies also provide evidence for an increased risk for other lymphoma types. In a pathological review of tumor materials from celiacs, there was an apparent aggregation of autoimmune and inflammatory disorders, female sex and B-cell lymphoma.\textsuperscript{76} More than double the risk for B-cell lymphoma was recorded with the most common type classified as a diffuse large B-cell lymphoma. In the same study, T-cell lymphomas had an approximate 50-fold risk along with a poorer prognosis (reflected in mean survival time after diagnosis and 5-year survival rate).\textsuperscript{76}

**LYMPHOMA TREATMENT**

Lymphoma treatment in celiac disease does not substantially differ from lymphoma treatment in the absence of celiac disease. Usually, surgery, radiation and chemotherapy have been used. Most believe that treatment results are best in those with an early diagnosis.\textsuperscript{77} Novel treatments, such as cladribine, a purine analogue that induces T-cell depletion,\textsuperscript{78} and alemtuzumab, a biological agent,\textsuperscript{79} along with autologous stem cell transplantation\textsuperscript{80} are being considered and evaluated.

Newly diagnosed lymphoma patients should be screened for celiac disease, especially if chronic diarrhea or weight loss are evident. A diagnosis of celiac disease is more readily established prior to lymphoma treatment (since chemotherapy or radiation may induce small intestinal changes). Concomitant recognition of underlying celiac disease may also have important nutritional implications.

**OTHER CANCERS**

Malignant disorders may occur elsewhere in the gastrointestinal tract in celiac disease. For some of these, the rate may be increased. Small bowel adenocarcinoma is normally rare, but may be more frequently recognized in celiac disease. Some have suggested that these may be due to an adenoma-carcinoma sequence,\textsuperscript{81} but others have reported that the risk of duodenal adenoma is not increased in celiac disease.\textsuperscript{81} Most occur in the proximal small intestine and may cause bleeding or obstruction. If complete resection can be accomplished, the prognosis is better than if a lymphoma were present.\textsuperscript{82}

Some European studies have also noted an increased risk of esophageal and pharyngeal carcinoma.\textsuperscript{53,83} This has not been confirmed in American centers, but in one report,\textsuperscript{57} a single hypopharyngeal squamous cell carcinoma was detected in a celiac patient with a prior lymphoma. In the same series, other esophageal or gastric cancers were not detected, in spite of repeated endoscopic studies during the course of diagnosis and treatment of celiac disease, but Barrett’s esophagus, a known precursor of esophageal adenocarcinoma, was reported.\textsuperscript{87} Possibly, environmental or other confounding factors in different geographic areas are responsible.

Colorectal cancer risk was marginally increased, mainly in the ascending and transverse colon,\textsuperscript{84} in a population-based celiac cohort, but not in the closely allied disorder, dermatitis herpetiformis.\textsuperscript{84} Other studies have not detected an increased colorectal cancer risk in celiac disease,\textsuperscript{55,57,85} especially in celiac disease with a diagnosis initially established late in life.\textsuperscript{55,57} Possibly, untreated celiac disease protects from colon cancer. Dietary fat or fat soluble agents, including hydrocarbons or other putative co-carcinogens that have been implicated in colon cancer pathogenesis, may be poorly absorbed and rapidly excreted. Alternatively, immunological changes (e.g., increased intraepithelial lymphocytosis) may prohibit development of epithelial malignancies. Further studies to elucidate this issue are needed.

**FUTURE DIRECTIONS**

Mechanisms involved in the development of malignancy in celiac disease are poorly understood, including both lymphoma as well as epithelial malignancies. The small intestinal mucosa involved with changes attributed to celiac disease may still show histological improvement with a gluten-free diet, even after intestinal lymphoma is detected.\textsuperscript{26,32} There are many potential confounding variables that may alter the pathogenesis of lymphoma in a celiac population and influence risk measurements in different countries. These include genetic, infectious (e.g., EB virus) and other dietary and epidemiological variables. Duration of gluten restriction and degree of compliance to a gluten-free diet are be specific factors that are difficult to measure precisely, but seem critical to malignant
change in celiac disease. Other malignancies, particularly epithelial malignancies, such as gastric or colon cancer, seem to occur much less often, even if celiac disease is only first recognized later in life. Possibly, untreated celiac disease protects against other cancers, such as colon cancer. Dietary fat or fat-soluble agents, such as hydrocarbons or other putative co-carcinogens, implicated in colon carcinogenesis may be poorly absorbed or rapidly excreted in celiac disease with diarrhea and impaired absorption. Immunological alterations, associated with increased intraepithelial lymphocyte numbers in celiac disease and the epithelial lymphocytosis reported in the stomach or colon of celiac,28,29 may directly or indirectly inhibit development of epithelial malignancies, particularly at these sites. Further studies are needed to elucidate these observations in adults with celiac disease.

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