Dig Dis Sci
DOI 10.1007/s10620-006-9240-z

ORIGINAL ARTICLE

Increased Risk of Papillary Thyroid Cancer in Celiac Disease

Laura Kent · Russell McBride · Robert McConnell · Alfred I. Neugut · Govind Bhagat · Peter H. R. Green

Received: 20 December 2005 / Accepted: 30 January 2006

Abstract Patients with celiac disease have an increased rate of malignancies that are not limited to lymphomas. Thyroid carcinoma has not previously been associated with celiac disease. However, among a cohort of patients with celiac disease, we identified an increased risk of papillary carcinoma of the thyroid, standard morbidity ratio of 22.52 (95% confidence interval 14.90–34.04; $P < .001$), compared to United States national surveillance data. These patients were on a gluten-free diet. Only 1 had Hashimoto's thyroiditis, suggesting that mechanisms apart from autoimmune thyroiditis contribute to the increased risk of carcinoma of the thyroid in celiac disease.

Keywords Celiac disease · Papillary carcinoma · Thyroiditis · Hashimoto's thyroiditis

L. Kent · R. McBride · R. McConnell · A. I. Neugut · P. H. R. Green (✉)
Department of Medicine, Columbia University College of Physicians and Surgeons,
161 Fort Washington Ave, Room 645, New York, 10032 New York, USA
e-mail: pg11@columbia.edu

G. Bhagat
Department of Pathology Columbia University College of Physicians and Surgeons,
New York, New York, USA

R. McBride · A. I. Neugut
Herbert Irving Comprehensive Cancer Center, Columbia University College of Physicians and Surgeons,
New York, New York, USA

R. McBride · A. I. Neugut
Department of Epidemiology, Mailman School of Public Health at Columbia University,
New York, New York, USA

Introduction

Compared to the general population, patients with celiac disease carry an increased burden of disease [1]. In addition to autoimmune diseases [2] and endocrine disorders [3], patients diagnosed with celiac disease have an increased risk of a variety of malignancies that include both T-cell and B-cell non-Hodgkin lymphoma, squamous carcinoma of the esophagus and oropharynx, and small intestinal adenocarcinoma [4–6]. In this report, we document a significantly increased risk of papillary carcinoma of the thyroid in patients with celiac disease.

Methods

We have maintained a database of patients diagnosed with celiac disease who were seen in our Celiac Disease Center since 1981. Data, including age at diagnosis, mode of presentation, adherence to the gluten-free diet, and other diagnoses, was prospectively entered into the database that was anonymized to protect privacy. Among these patients we identified 606, seen between July 1981 and April 2004, who had biopsy-proven celiac disease.

The prevalence of papillary thyroid cancer in our database was compared to data in the Surveillance, Epidemiology and End Point Results (SEER) program of the National Cancer Institute, Washington, D.C. [7]. Information was accessed using Surveillance Research Program, National Cancer Institute SEER*Stat software(available: www.seer.cancer.gov/seerstat) version 6.1.

Patient-years at risk were calculated from the date of diagnosis of celiac disease to either the date of diagnosis of cancer or the date of the most recent follow-up visit, whichever came first. We calculated the standardized morbidity ratio

Table 1 Results

Expected prevalence of papillary thyroid cancer based on SEER data	0.133	22/100,000
Observed prevalence of papillary thyroid cancer in our cohort of celiac disease patients	3	494/100,000

Note. SMR = 22.52; 95% CI 14.90–34.04; $P < .001$.

(SMR), ratio of observed to expected and 95% confidence intervals (CI), assuming that the observed number of cancers had a Poisson distribution. Histopathology of thyroid cancer was reviewed. The study was approved by the Institutional Review Board of Columbia University.

Results

The database consisted of 606 patients; 68% were female and the age at diagnosis of celiac disease was 41.5 ± 17.6 years. The prevalence of thyroid disease was 18.4%. The classical diarrhea-predominant presentation of celiac disease was noted in 43%. Three of these patients had papillary thyroid cancer, whereas only 0.133 patients were expected, resulting in a SMR of 22.52 (95% CI 14.90–34.04; $P < .001$; Table 1). The prevalence for papillary thyroid cancer was 494 per 100,000 compared to 22 per 100,000 of the general population.

Of the patients with papillary thyroid cancer (Table 2), 2 were female and 1 male; the age at diagnosis of cancer was 44.3 years (range, 38–48 years), and mean duration since diagnosis of celiac disease 7.7 years (range, 1–19.4 years). Each had originally presented with diarrhea-predominant, symptomatic celiac disease and responded to a gluten-free diet. Adherence to the diet was strict as confirmed by an examination of the dietary history by an experienced dietician and negative celiac serologies. None of the patients had a family history of thyroid cancer or a history of exposure to radiation. Each patient presented with a thyroid nodule or mass and was euthyroid, although one had positive thyroid antibodies.

Two patients underwent total thyroidectomy and one hemithyroidectomy. One of the patients had a follicular variant of papillary thyroid carcinoma, 2 patients had multifocal and bilateral tumors, and 2 patients had lymph node involvement. Hashimoto's thyroiditis (as defined histologically because of the presence of diffuse lymphocytic and plasma cell infiltration with formation of lymphoid follicles, damage to the follicular basement membrane, and Hurthle cell change of the thyroid follicular epithelium) was identified in the resected nonmalignant thyroid tissue in only 1 patient, who had the positive thyroid antibodies.

Table 2 Patients With Celiac Disease and Papillary Thyroid Cancer

Female	2/3 (67%)
Mean age (y) at papillary thyroid cancer diagnosis	44 (range, 34–48)
Mean duration since diagnosis of celiac disease (y)	7.7
Diarrhea as presenting symptom of celiac disease (%)	100
Adherence to gluten-free diet (%)	100

Discussion

We observed a significantly increased risk of papillary thyroid cancer in our cohort of patients with celiac disease compared to United States national SEER data. This occurred despite adherence to a gluten-free diet that is considered protective against the development of malignancies [4]. One of the patients was on the diet for only 1 year.

Thyroid disease, especially Hashimoto's thyroiditis, is common in patients with celiac disease [3]. Papillary thyroid cancer occurs frequently in the setting of Hashimoto's thyroiditis [8, 9]. Because clinically significant papillary thyroid cancer is observed in fewer patients with Hashimoto's thyroiditis than those who harbor precursor lesions [9], it is likely that additional mutagenic events or immune mechanisms might play important roles in papillary thyroid cancer development. Because only 1 of our patients had Hashimoto's thyroiditis, additional mechanisms apart from autoimmune thyroiditis may be important for the development of papillary thyroid cancer in patients with celiac disease. Such mechanisms could include chronic genotoxic stress owing to chronic inflammation mediated by the lymphocytic infiltrates and/or alternatively an as-yet uncharacterized immune deregulation could lead to ineffective tumor surveillance and indirectly lead to an increased incidence of malignancies [10].

Thyroid cancer has not previously been reported as an associated malignancy in series of adult patients with celiac disease [5, 6, 11–15]. However, there were thyroid cancers among a European series of children with celiac disease and malignancies [16]; Freeman [17] has reported a thyroid lymphoma in a patient with celiac disease. Our patients were seen in a specialist referral setting that may have biased the results. In addition, we are not aware of any regional factor that could have influenced the increased occurrence of thyroid cancer in these patients. However, this study should alert clinicians to be aware of an increased risk of papillary thyroid cancer in patients with celiac disease. Examination of the thyroid should be performed as part of the regular physical examination, and thyroid nodules should be evaluated by ultrasonography and biopsy, to exclude thyroid cancer.

References

1. Green PH, Jabri B (2003) Coeliac disease. Lancet 362:383–391
2. Bai D, Brar P, Holleran S, Ramakrishnan R, Green PH (2005) Effect of gender on the manifestations of celiac disease: Evidence for greater malabsorption in men. Scand J Gastroenterol 40:183–187
3. Collin P, Kaukinen K, Valimaki M, Salmi J (2002) Endocrinological disorders and celiac disease. Endocr Rev 23:464–483
4. Holmes GK, Prior P, Lane MR, Pope D, Allan RN (1989) Malignancy in coeliac disease—Effect of a gluten free diet. Gut 30:333–338
5. Green PH, Fleischauer AT, Bhagat G, Goyal R, Jabri B, Neugut AI (2003) Risk of malignancy in patients with celiac disease. Am J Med 115:191–195
6. Askling J, Linet M, Gridley G, Halstensen TS, Ekstrom K, Ekbom A (2002) Cancer incidence in a population-based cohort of individuals hospitalized with celiac disease or dermatitis herpetiformis. Gastroenterology 123:1428–1435
7. Surveillance E, and End Results (SEER) Program (2004) SEER*Stat Database: Incidence-SEER 9 Regs Public-Use. In: National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch. www.seer.cancer.gov.
8. Singh B, Shaha AR, Trivedi H, Carew JF, Poluri A, Shah JP (1999) Coexistent Hashimoto's thyroiditis with papillary thyroid carcinoma: Impact on presentation, management, and outcome. Surgery 126:1070–1076
9. Prasad ML, Huang Y, Pellegata NS, de la Chapelle A, Kloos RT (2004) Hashimoto's thyroiditis with papillary thyroid carcinoma (PTC)-like nuclear alterations express molecular markers of PTC. Histopathology 45:39–46
10. de Visser KE, Eichten A, Coussens LM (2006) Paradoxical roles of the immune system during cancer development. Nat Rev Cancer 6:24–37
11. Holmes GK, Stokes PL, Sorahan TM, Prior P, Waterhouse JA, Cooke WT (1976) Coeliac disease, gluten-free diet, and malignancy. Gut 17:612–619
12. Selby WS, Gallagher ND (1979) Malignancy in a 19-year experience of adult celiac disease. Dig Dis Sci 24:684–688
13. Cooper BT, Holmes GK, Ferguson R, Cooke WT (1980) Celiac disease and malignancy. Medicine (Baltimore) 59:249–261
14. Holmes GK (1997) Celiac disease and malignancy. J Pediatr Gastroenterol Nutr 24:S20–S23
15. Peters U, Askling J, Gridley G, Ekbom A, Linet M (2003) Causes of death in patients with celiac disease in a population-based Swedish cohort. Arch Intern Med 163:1566–1572
16. Schweizer JJ, Oren A, Mearin ML (2001) Cancer in children with celiac disease: A survey of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 33:97–100
17. Freeman HJ (2000) T cell lymphoma of the thyroid gland in celiac disease. Can J Gastroenterol 14:635–636