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ABOUT COVER

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ORIGINAL ARTICLE

Observational Study

Prevalence of malignant neoplasms in celiac disease patients - a nationwide United States population-based study

Maryam Bilal Haider, Ali Al Sbihi, Sushmitha Nanja Reddy, Peter Green

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Abstract

BACKGROUND

Celiac disease (CeD) is an autoimmune disorder triggered by the immune response to gluten in genetically predisposed individuals. Recent research has unveiled a heightened risk of developing specific malignant neoplasms (MN) and various malignancies, including gastrointestinal, lymphomas, skin, and others, in individuals with CeD.

AIM

To investigate the prevalence of MN in hospitalized CeD patients in the United States.

METHODS

Using data from the National Inpatient Sample spanning two decades, from January 2000 to December 2019, we identified 529842 CeD patients, of which 78128 (14.75%) had MN. Propensity score matching, based on age, sex, race, and calendar year, was employed to compare CeD patients with the general non-CeD population at a 1:1 ratio.

RESULTS

Positive associations were observed for several malignancies, including small intestine, lymphoma, nonmelanoma skin, liver, melanoma skin, pancreas myelodysplastic syndrome, biliary, stomach, and other neuroendocrine tumors

(excluding small and large intestine malignant carcinoid), leukemia, uterus, and testis. Conversely, CeD patients exhibited a reduced risk of respiratory and secondary malignancies. Moreover, certain malignancies showed null associations with CeD, including head and neck, nervous system, esophagus, colorectal, anus, breast, malignant carcinoids, bone and connective tissues, myeloma, cervix, and ovary cancers.

CONCLUSION

Our study is unique in highlighting the detailed results of positive, negative, or null associations between different hematologic and solid malignancies and CeD. Furthermore, it offers insights into evolving trends in CeD hospital outcomes, shedding light on advancements in its management over the past two decades. These findings contribute valuable information to the understanding of CeD's impact on health and healthcare utilization.

Key Words: Celiac disease; Malignant neoplasm; Autoimmune disorder; Hospitalized patients; Healthcare utilization; Gastrointestinal malignancies; Lymphomas; Epidemiology

Core Tip: This study from National Inpatient Sample database presents one of the largest studied cohort of celiac disease (CeD) and present significant insights into the association between CeD and various malignancies, including gastrointestinal, genitourinary, hematologic, and gynecologic cancers. Interestingly, CeD patients exhibit a reduced risk of respiratory malignancies. Variations in hospital outcomes, such as length of stay, cost of care, and inpatient mortality, highlight the complex relationship between CeD and malignancies. The study underscores the importance of recognizing this relationship, emphasizing the need for vigilant screening in CeD patients, particularly for specific malignancies like small intestine, lymphoma, and skin cancers. These findings contribute to refining CeD management and understanding broader healthcare trends over two decades.

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INTRODUCTION

Celiac disease (CeD) is an autoimmune, inflammatory condition developed in genetically predisposed individuals due to the immune response to the gluten component of wheat[1]. The most recent global prevalence of CeD is 1.4% based on serological markers and 0.7% confirmed through histological examination[2]. This disease is characterized by the presence of specific autoantibodies in the bloodstream and distinct pathological changes in the small intestine, including villous atrophy, crypt hypertrophy, and an increase in intraepithelial lymphocytes[3]. What sets CeD apart is that by avoiding gluten, its progression can be halted, and mucosal damage can even be reversed[4].

Individuals with CeD are at an elevated risk of developing other autoimmune conditions, such as autoimmune thyroiditis, type 1 diabetes mellitus, Addison's disease, and various other disorders[5]. Furthermore, there is a well-established heightened risk of malignancies among CeD patients. Recent research has shown that CeD increases the likelihood of developing specific cancers, including gastrointestinal, lymphomas, skin cancers, and others[6,7]. Studies have indicated that the risk of cancer is most pronounced within the first year after diagnosis and subsequently decreases, likely due to better adherence to a gluten-free diet. Therefore, early diagnosis and gluten avoidance may reduce the risk of such complications[8,9].

Geographic differences in the occurrence of malignancies among individuals with CeD have been observed[10]. However, there is a lack of population-based studies on the connection between CeD and cancer in the United States. In this study, we investigate the prevalence of malignant neoplasms (MN) in CeD patients admitted to hospitals in the United States. We analyze the significance of the association between MN and CeD, categorized by the type of cancer, using a national inpatient database comprising 529842 CeD patients. The second part of our research explores hospital outcomes, including detailed mortality data, length of hospital stays, and the cost of care in CeD patients both with and without MN.

MATERIALS AND METHODS

Data source

We employed data from the National (Nationwide) Inpatient Sample (NIS) database spanning a two-decade period from January 2000 to December 2019. The NIS is an integral component of the Healthcare Cost and Utilization Project (HCUP),

a collaborative initiative established through a Federal-State partnership and financially supported by the Agency for Healthcare Research and Quality (AHRQ). This database stands as the most extensive publicly accessible repository of inpatient care information, encompassing over seven million hospital admissions and representing a 20% stratified sample of all hospital discharges across the United States[11].

Within this dataset, a comprehensive array of patient demographic details, clinical information (including diagnoses and procedure codes), and data pertaining to hospital utilization and outcomes are included. The diagnostic coding system employed in the dataset adhered to the International Classification of Diseases, 9th Edition (ICD-9) until the third quarter of 2015, after which it transitioned to the ICD-10 system in September 2015[12]. Importantly, it is noteworthy that HCUP databases align with the definition of limited datasets, and in accordance with the Health Insurance Portability and Accountability Act, no International Review Board review is necessitated for limited datasets[13].

Study population

Patient and hospital characteristics, along with outcomes and resource utilization data, were retrieved from the NIS database using ICD codes (see Supplementary Table 1). Individuals who were admitted with either the primary or secondary diagnosis of CeD, as indicated by ICD-9 code 579.0 or ICD-10 code K90.0, were included in the case group. The case group underwent matching, aligning with individuals from the non-CeD general population in a 1:1 ratio based on age, sex, race, and calendar year, utilizing the nearest neighbor propensity score method. Detailed information about the progression of cases and controls to compare the prevalence of MN is shown in Figure 1.

Additionally, we conducted a comparison of hospital outcomes between individuals with MN who had CeD and those without it. The group without CeD but with MN was carefully chosen from the general population, employing a 1:1 nearest neighbor propensity score matching technique based on age, sex, race, calendar year, and precise matching regarding the type of malignant neoplasm. Figure 2 provides a visual representation of the process outlining the development of cohorts with and without CeD in the context of MN.

Outcome measures

We conducted a comparison of the occurrence of MN in individuals with CeD, referred to as cases, against a matched group without CeD, referred to as controls. We examined the demographic characteristics of CeD patients, including age, sex, race, and socioeconomic status, in the context of the presence or absence of MN. The NIS dataset included socioeconomic status information, which was categorized by dividing the median household income in the patient's zip code into quartiles for each year.

Furthermore, we conducted a comparison of hospital-related outcomes among individuals with CeD who had MN and matched them against those without CeD. The matching process was based on age, sex, race, year, and the specific profile of MN. We assessed various aspects of hospital outcomes, which encompassed inpatient mortality, the length of hospital stays, and the overall charges incurred. To ensure accuracy, the total cost of care was adjusted using the Consumer Price Index from the United States Bureau of Labor Statistics[14].

Statistical analyses

Data processing was conducted using R (Studio 1.4), and statistical analyses were performed using SAS (SAS Institute, Cary, NC, United States). We executed one-to-one propensity score matching employing the "Matchit" package in R, employing nearest neighbor and exact matching techniques. Nominal variables were presented using frequency distributions, while continuous variables were summarized with means and standard deviations.

To compare the prevalence of MN in CeD patients with and without CeD, we utilized the χ^2 test. Group comparisons of continuous variables were carried out using the Student *t*-test and the Rao-Scott χ^2 test, accounting for the weighted sample in the analysis. We adhered to the year-specific AHRQ recommendations and adjusted the weights for years up to 2012[15]. Age was categorized into five groups for group-level comparisons: < 18; 18-49; 49-59; 59-69; and ≥ 70 years. In instances where race and socioeconomic status data were missing, they were categorized as "other".

For assessing temporal trends, we employed the Cochran-Armitage trend test for nominal variables and Poisson regression with a log link for continuous variables. Outliers and missing values in the length of stay (LOS) and total charges were excluded from the hospital outcomes analysis. Hypothesis testing was conducted with a two-tailed approach, and statistical significance was established at a P value < 0.05.

RESULTS

Baseline characteristics of the study population

The baseline characteristics of the CeD patients with and without MN are shown in Table 1. We found 529842 CeD patients from January 2000 to December 2019 in weighted NIS, of which 78128 (14.75%) had MN. Among the CeD patients, those who had MN were older, with a mean age of 68 (± 16) years as compared to a mean age of 53 (± 22) years in CeD without MN with P value < 0.0001, more males (36% among CeD with MN *vs* 28% among CeD without MN) than females (64% among CeD with MN *vs* 72% among CeD without MN) with P value < 0.0001, frequent in the Caucasian race (84% among CeD with MN *vs* 79% among CeD without MN) than African American race (1.90% among CeD with MN *vs* 2.96% among CeD without MN) with P value < 0.0001.

Table 1 Comparison between patient's characteristics of celiac disease patients with and without malignant neoplasms, National Inpatient Sample 2000-2019

	Overall CeD patients	CeD without MN, weighted, *n* (%)	CeD with MN, weighted, *n* (%)	*P* value
Weighted total	529842	451714 (85.25)	78128 (14.75)	
Sex				< 0.0001[2]
Female	374102 (70.61)	323904 (71.70)	50199 (64.25)	
Male	155739 (29.39)	127810 (28.30)	27929 (35.75)	
Age (year), mean ± SD	55.34 ± 22.17	53.08 ± 22.40	67.66 ± 15.94	< 0.0001[1]
Age groups (year)				< 0.0001[3]
< 18	30807 (5.82)	29910 (6.62)	898 (1.15)	
18-49	168411 (31.79)	159531 (35.31)	8880 (11.35)	
49-59	75661 (14.28)	65080 (14.42)	10581 (13.54)	
59-69	85753 (16.18)	68589 (15.18)	17164 (21.96)	
≥ 70	169209 (31.93)	128604 (28.47)	40605 (51.97)	
Race/ethnicity				< 0.0001[3]
White	421882 (79.64)	356333 (78.88)	65549 (83.90)	
Black	14876 (2.81)	13386 (2.96)	1490 (1.90)	
Hispanic	20834 (3.93)	18657 (4.13)	2177 (2.78)	
Asian or Pacific Islander	2746 (0.51)	2462 (0.55)	284 (0.36)	
Native American	1698 (0.32)	1501 (0.33)	197 (0.25)	
Other	67806 (12.79)	59375 (13.14)	8431 (10.79)	
Median household income for patient's zip code				< 0.0001[3]
0-25th percentile	91079 (17.19)	79152 (17.52)	11927 (15.26)	
26th to 50th percentile (median)	125043 (23.60)	107046 (23.70)	17997 (23.05)	
51st to 75th percentile	143974 (27.17)	122501 (27.12)	21472 (27.48)	
76th to 100th percentile	160727 (30.34)	135206 (29.93)	25521 (32.66)	
Other	9019 (1.70)	7807 (1.73)	1211 (1.55)	

[1]Two sample Student *t*-test, 2-tailed for comparing means of two continuous variables.
[2]Rao-Scott χ^2, 2-tailed test for the association of two categorical variables.
[3]Rao-Scott χ^2, 2-tailed test for two by *n* table. Statistical significance illustrates that the two groups differ.
CeD: Celiac disease; MN: Malignant neoplasm.

Risk of cancer in CeD

Table 2 compared the prevalence of MN in CeD (cases) and matched (age, sex, and race) non-CeD patients in NIS from 2000 to 2019. As compared to non-CeD patients, CeD patients are at heightened risk of small intestine [odds ratio (OR) = 7.71; 95% confidence interval (CI): 5.0-11.9; $P < 0.0001$], lymphoma (OR = 2.06; 95%CI: 1.90-2.23; $P < 0.0001$), other gastrointestinal (GI) organs (OR = 2.02; 95%CI: 1.41-2.92; $P < 0.0001$), nonmelanoma skin (OR = 1.97; 95%CI: 1.81-2.16; $P < 0.0001$), thyroid (OR = 1.84; 95%CI: 1.58-2.13; $P < 0.0001$), liver (OR = 1.83; 95%CI: 1.49-2.24; $P < 0.0001$), melanoma skin (OR = 1.54; 95%CI: 1.35-1.76; $P < 0.0001$), pancreas (OR = 1.53; 95%CI: 1.29-1.80; $P < 0.0001$), myelodysplastic syndrome (OR = 1.84; 95%CI: 1.55-2.17; $P < 0.0001$), biliary (OR = 1.39; 95%CI: 1.01-1.91; $P = 0.045$), stomach (OR = 1.35; 95%CI: 1.08-1.69; $P < 0.0.005$), other neuroendocrine tumors (excluding small and large intestine malignant carcinoid) (OR = 1.48; 95%CI: 1.03-2.12; $P = 0.031$), leukemia (OR = 1.13; 95%CI: 1.02-1.25; $P = 0.02$), uterus (OR = 1.17; 95%CI: 1.03-1.32; $P = 0.013$), prostate (OR = 1.14; 95%CI: 1.06-1.23; $P < 0.001$), and testis (OR = 1.50; 95%CI: 1.07-2.10; $P = 0.018$). The bar chart in Supplementary Figure 1 also showed the prevalence comparison of MN positively associated with CeD.

Conversely, individuals with CeD exhibit a notably reduced risk of developing respiratory malignancies (OR = 0.68; 95%CI: 0.63-0.73; $P < 0.0001$) and secondary malignancies (OR = 0.76; 95%CI: 0.73-0.81; $P < 0.0001$). Furthermore, our analysis did not reveal any significant association between CeD and the occurrence of malignancies affecting the head and neck, nervous system, esophagus, colorectal, anus, breast, malignant carcinoids, bone and connective tissues,

Table 2 Prevalence of malignant neoplasms in celiac disease *vs* matched (age-, sex-, race) non-celiac disease patients, National Inpatient Sample 2000-2019

Neoplasm type	CeD cases	CeD controls	OR (95%CI)	*P* value
	Unweighted (*n* = 108052), 50%, *n* (%)	Unweighted (*n* = 108052), 50%, *n* (%)		
All malignant neoplasm	15884 (14.70)	14125 (13.07)	1.15 (1.12-1.18)	< 0.0001
Positive association				
Stomach	179 (0.17)	133 (0.12)	1.35 (1.08-1.69)	0.0092
Small intestine	177 (0.16)	23 (0.02)	7.71 (5.0-11.9)	< 0.0001
Liver	261 (0.24)	143 (0.13)	1.83 (1.49-2.24)	< 0.0001
Biliary	90 (0.08)	65 (0.06)	1.39 (1.01-1.91)	0.0446
Other GI organs	87 (0.08)	43 (0.04)	2.02 (1.41-2.92)	< 0.0001
Thyroid	474 (0.44)	259 (0.24)	1.84 (1.58-2.13)	< 0.0001
Pancreas	358 (0.33)	235 (0.22)	1.53 (1.29-1.80)	< 0.0001
Melanoma skin	552 (0.51)	359 (0.33)	1.54 (1.35-1.76)	< 0.0001
Nonmelanoma skin (all other skin excluding melanoma)	1441 (1.33)	735 (0.68)	1.97 (1.81-2.16)	< 0.0001
Other neuroendocrine tumors	74 (0.07)	50 (0.05)	1.48 (1.03-2.12)	0.0311
Lymphoma	1861 (1.72)	912 (0.84)	2.06 (1.90-2.23)	< 0.0001
Leukemia	835 (0.77)	742 (0.69)	1.13 (1.02-1.25)	0.0187
Myelodysplastic syndrome	397 (0.37)	216 (0.20)	1.84 (1.55-2.17)	< 0.0001
Uterus	562 (0.52)	482 (0.45)	1.17 (1.03-1.32)	0.0131
Prostate	1421 (1.32)	1247 (1.15)	1.14 (1.06-1.23)	0.0007
Testis	84 (0.08)	56 (0.05)	1.50 (1.07-2.10)	0.0179
Negative association				
Respiratory	1244 (1.15)	1813 (1.68)	0.68 (0.63-0.73)	< 0.0001
Secondary malignancies	2199 (2.04)	2846 (2.63)	0.76 (0.73-0.81)	< 0.0001
Urinary	952 (0.88)	1053 (0.97)	0.90 (0.83-0.99)	0.0234
Null association				
Head and neck	272 (0.25)	314 (0.29)	0.87 (0.74-1.02)	0.0823
Nervous system	227 (0.21)	257 (0.24)	0.88 (0.74-1.06)	0.1722
Esophagus	152 (0.14)	125 (0.12)	1.22 (0.96-1.54)	0.1045
Colorectal	1752 (1.62)	1774 (1.64)	0.99 (0.93-1.06)	0.7087
Anus	21 (0.02)	26 (0.02)	0.81 (0.45-1.44)	0.4658
Breast	2844 (2.63)	2919 (2.70)	0.98 (0.92-1.03)	0.3166
Other endocrine (excluding thyroid and pancreas)	25 (0.02)	30 (0.03)	0.83 (0.49-1.41)	0.5001
Malignant carcinoid tumor - small intestine	14 (0.01)	13 (0.01)	1.08 (0.51-2.29)	0.8474
Malignant carcinoid tumor - large intestine	5 (0.005)	6 (0.005)	0.83 (0.25-2.73)	0.7630
Bone and connective tissues	134 (0.12)	161 (0.15)	0.83 (0.66-1.04)	0.1157
Myeloma	313 (0.29)	274 (0.25)	1.14 (0.97-1.34)	0.1070
Cervix	448 (0.41)	418 (0.39)	1.07 (0.94-1.22)	0.3070
Ovary	472 (0.44)	430 (0.40)	1.10 (0.96-1.25)	0.1611
Other female genital organs	126 (0.12)	139 (0.13)	0.91 (0.71-1.15)	0.4242

Other male genital organs	11 (0.01)	4 (0.004)	2.75 (0.88-8.63)	0.0707

CeD: Celiac disease; OR: Odds ratio; CI: Confidence interval; GI: Gastrointestinal.

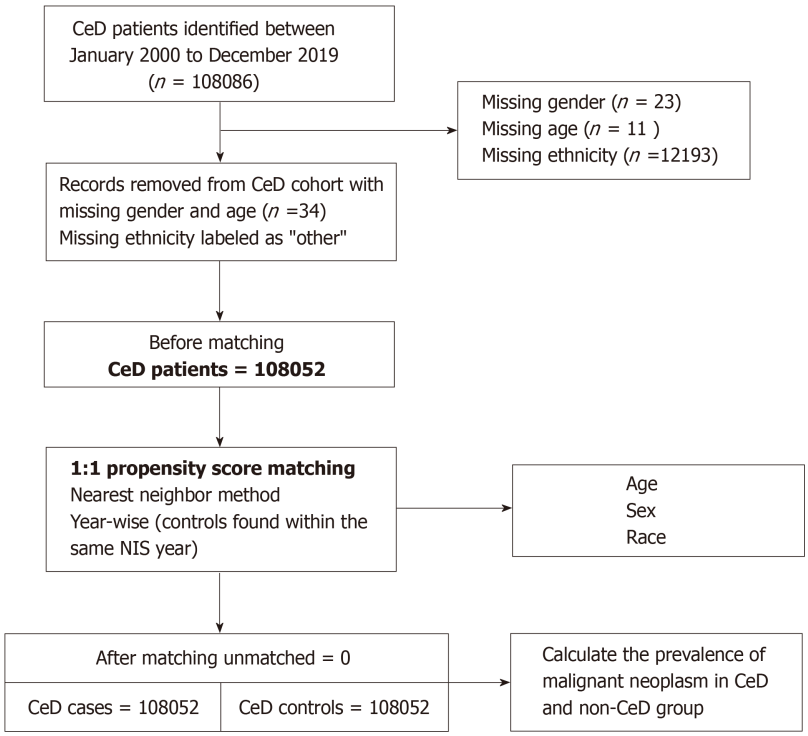

Figure 1 Flow diagram outlining the cases and controls for comparing the prevalence of malignant neoplasm in celiac disease and non-celiac disease patients. CeD: Celiac disease.

myeloma, cervix, or ovary.

Hospital outcomes of MN with vs without CeD

Figure 3 and Table 3, provide a comparative analysis of hospital outcomes and resource utilization. This assessment includes mortality rates, length of hospitalization, and the overall cost of care, and it contrasts patients with CeD who have MN with a matched group of patients without CeD but with MN. The matching process is based on age, sex, race, and the specific type of malignant neoplasm. The mean differences in length of the stay and total cost of care are found to be higher in CeD cohort (0.21 days; 99%CI: 0.05-0.38; $P < 0.001$) and ($3172; 99%CI: $1467-$4878; $P < 0.001$), respectively. However, the inpatient mortality is lower in CeD with MN than non-CeD with MN (0.72; 99%CI: 0.61-0.86; $P < 0.001$). Supplementary Figure 2 illustrated the trend in the total cost of care for hospitalized CeD patients with MN, compared to non-CeD patients with MN.

DISCUSSION

Utilizing the NIS dataset, which offers a representative sample of the United States population, our investigation revealed that individuals with CeD exhibited a notably heightened incidence of at least sixteen distinct MN. The most significant increase was observed in cases of small intestinal adenocarcinomas, with an OR of 7.7, followed by lymphomas (OR = 2.06) and other malignancies affecting the GI organs (OR = 2.01). Conversely, a reduced risk was identified for respiratory MNs. This study aligns with some findings from previous research while also highlighting notable disparities.

The initial documentation of malignancy in individuals with CeD dates back to 1965 when a case of small intestinal adenocarcinoma was reported in France[16]. Subsequently, during the late 1960s, research investigating the connection between CeD and the development of malignancies began to emerge[17,18]. Over the ensuing decades, a series of research studies conducted in Europe provided substantial evidence supporting the association between CeD and MN [19-22]. Likewise, a study conducted in the United States observed a heightened risk of MNs in a limited cohort of CeD patients compared to the general American population[23]. Various investigations have highlighted that the risk of MN development is notably higher in the early stages following the diagnosis of CeD. However, as time progresses, the Standardized Incidence Ratio (SIR) for MNs tends to decrease and may even become statistically nonsignificant after the initial year of diagnosis or in subsequent years[24-26]. Additionally, some studies have demonstrated that individuals

Table 3 Comparison of inpatient mortality, mean total charges, and length of stay in celiac disease patients with malignant neoplasms *vs* matched non-celiac disease with malignant neoplasm (matched by age-, sex-, race-, and malignant neoplasm profile), National Inpatient Sample 2000-2019

	Mortality		Length of stay		Total charges	
	OR (99%CI)	*P* value	Mean difference (99%CI)	*P* value	Mean (99%CI)	*P* value
CeD with MN	0.72 (0.61-0.86)	< 0.0001[1]	0.21 (0.05-0.38)	0.0006[2]	$3172, $1467-$4878	< 0.0001[2]
Matched non-CeD with MN	Reference	NA	Reference	NA	Reference	NA

[1]χ^2, 2-tailed test for the association of two categorical variables.
[2]Two sample Student *t*-test, 2-tailed for comparing means of two continuous variables.
CeD: Celiac disease; MN: Malignant neoplasm; OR: Odds ratio; CI: Confidence interval; NA: Not available.

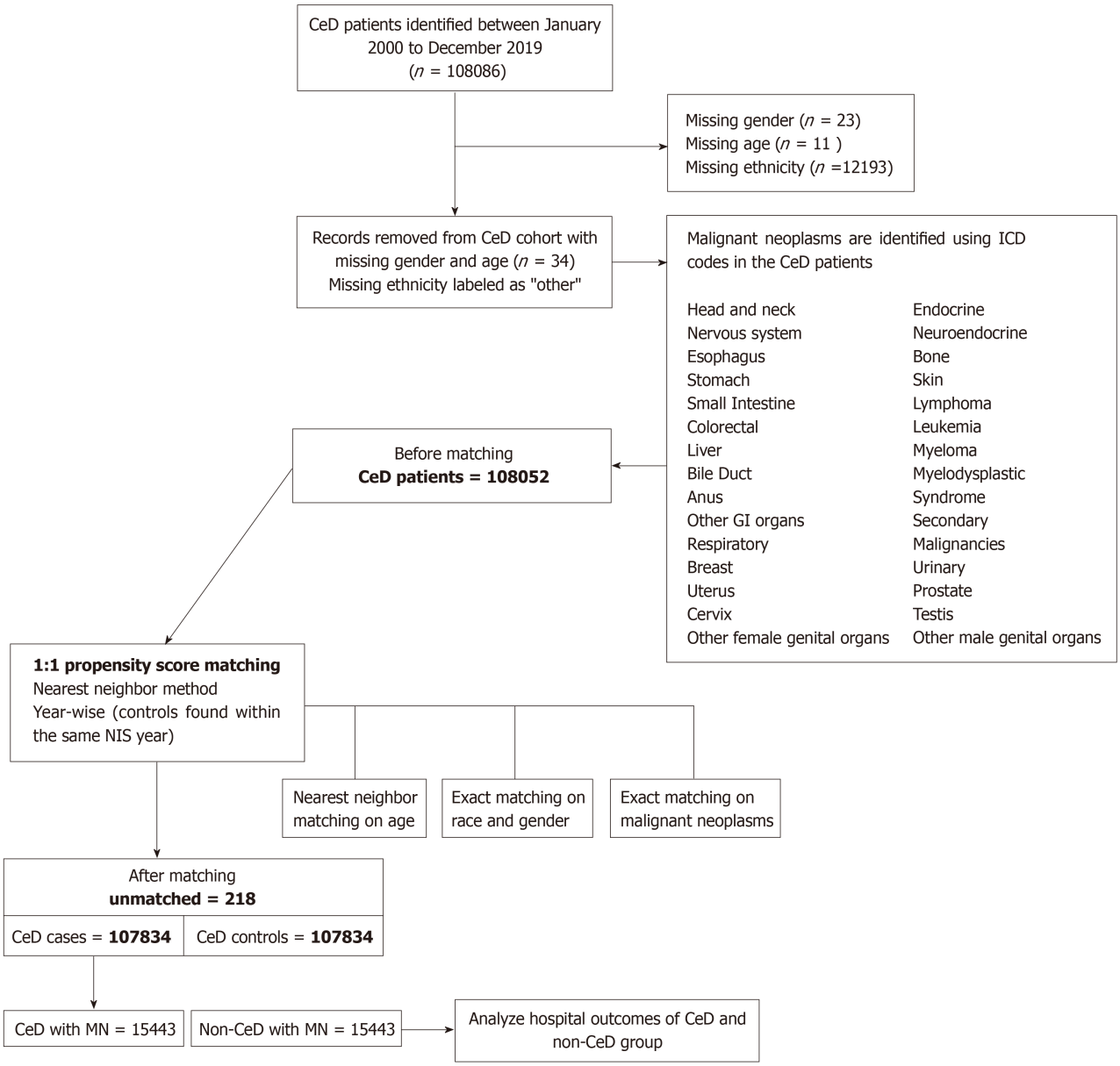

Figure 2 Flow diagram outlining the cases and controls for comparing the hospital outcomes of celiac disease with malignant neoplasm *vs* non-celiac disease with malignant neoplasm. CeD: Celiac disease; NIS: National Inpatient Sample; MN: Malignant neoplasm.

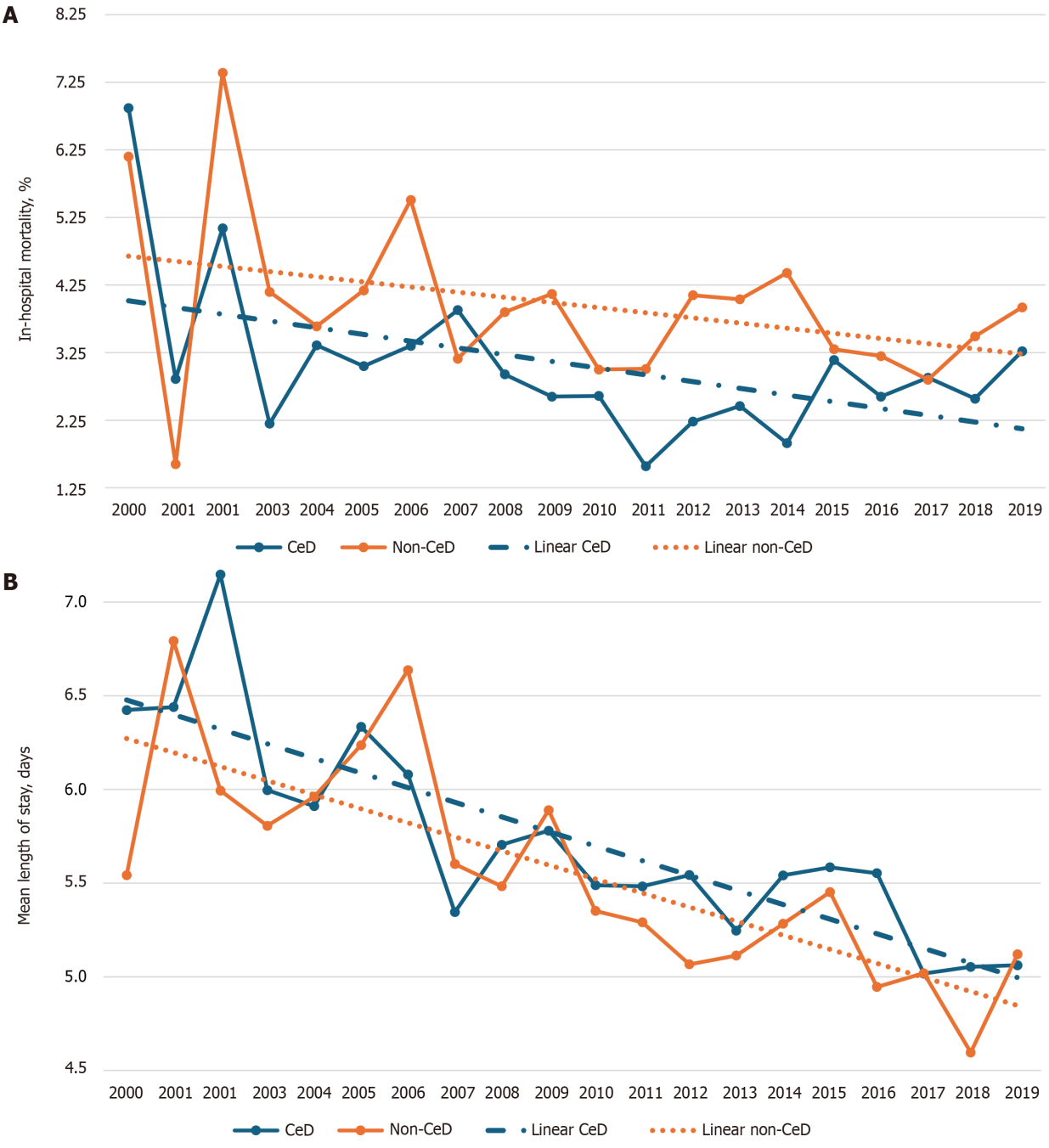

Figure 3 Trend of in-hospital mortality and the mean length of stay of hospitalized of celiac disease patients with malignant neoplasm *vs* matched non-celiac disease with malignant neoplasm (matched by age-, sex-, race-, and corresponding malignant neoplasm), National Inpatient Sample 2000-2019. A: Trend of in-hospital mortality of celiac disease (CeD) patients with malignant neoplasm (MN) *vs* matched non-CeD with MN; B: Trend of the mean length of stay of hospitalized CeD patients with MN *vs* matched non-CeD with MN. CeD: Celiac disease.

with CeD experience elevated mortality rates in the initial years following diagnosis, potentially linked to malignancies [27-30]. Notably, adherence to a gluten-free diet emerges as a robust protective factor against the development of malignancies[8,31]. A study underscores that mortality rates are significantly higher among patients with delayed diagnoses or severe symptoms at the time of diagnosis[29].

The precise pathogenic mechanism underlying malignancy development in CeD remains an enigma[32]. Several factors, including but not limited to persistent inflammation, the release of proinflammatory cytokines, continual antigen stimulation, cytokine surges, heightened susceptibility to carcinogens, and nutritional deficiencies induced by the disease or the adoption of a gluten-free diet, have all been proposed as potential contributors to the onset of malignancies[23,33].

Among the malignancies exhibiting a positive association with CeD, our findings indicate that lymphomas have the highest prevalence and the second-highest OR within the CeD sample. The connection between CeD and the development of lymphomas and lymphoproliferative malignancies has been the subject of long-standing investigation in scientific literature[34-36]. For instance, a study conducted by Green *et al*[23], which focused on the period from 1981 to 2000 and involved 381 patients with CeD at a referral center in New York, revealed a noteworthy 9-fold elevated risk of

non-Hodgkin's lymphoma (NHL). NHL emerged as the most prevalent MN in CeD patients. Importantly, all NHL patients in the study reported strict adherence to a gluten-free diet for an average of 5 years[23]. This observation aligns with similar findings reported in other studies[37,38].

Two Swedish studies, one involving roughly 11000 CeD patients and the other with approximately 11650 CeD patients, reported SIR of 6.3 (95%CI: 4.2-125)[31] and 6.6 (95%CI: 5.0-8.6) for NHL[38]. Furthermore, Elfström *et al*[39] research suggested that the risk of lymphoproliferative malignancies was similar between CeD patients with only positive serology and those without documented inflammation, compared to the general population. Additionally, earlier investigations have identified relative risks (RR) ranging from 3 to 100 for various lymphoma subtypes in the context of CeD[8,31,38,40,41]. The prevalence of enteropathy-associated T-cell lymphoma (EATL), a rare tumor, has attracted research attention alongside the increasing incidence of CeD in recent decades[42-44]. Typically, EATL has been linked to refractory CeD, which is characterized by the persistent or recurrent pathological manifestations of CeD despite stringent adherence to a gluten-free diet[45,46]. Notably, in regions of Northern Europe where CeD is more widespread, EATL type 1 (pleomorphic and anaplastic, typically CD56 negative, with gains in chromosomes 1q and 5q) prevails over EATL type 2 (medium-sized cancer cells, typically CD56 positive, with oncogene MYC gain), which is more commonly observed in Asian countries[47-50]. It is notable that there is no clear causality on the exact mechanism of how CeD patients develop lymphoma, the main hypothesis is that as an autoimmune disease with immunity overactivation, persistent inflammation, villous atrophy, and intestinal mucosal healing resulting in aberrant lymphocytes' hyperproliferation can result in a possibility of malignant transformation of intraepithelial lymphocytes causing lymphomas[51-53]. Numerous studies have reported the occurrence of both T and B cell lymphomas in individuals with CeD[39,54-56]. In terms of prognosis, research has indicated that CeD patients face a roughly 0.15% elevated risk of NHL-related mortality in the decade following diagnosis[57]. It is also notable that T-cell lymphomas tend to exhibit a poorer prognosis in comparison to B-cell lymphomas[58,59].

Our findings indicate that small bowel carcinomas (SBC) exhibit the highest OR of 7.71 (95%CI: 5.0-11.9) among MN, demonstrating a positive correlation with CeD. SBC is a rare malignancy in the general population, and its association with CeD is firmly established. This connection was initially documented by Swinson *et al*[22], revealing a RR of 82.6 for SBC development in individuals with CeD. Over subsequent decades, several significant studies have reaffirmed this association. Elfström *et al*[60] in a prospective analysis encompassing more than 45000 CeD patients, reported an average hazard ratio (HR) for SBC development ranging from 2.22 to 4.67, stratified based on CeD marsh classification or positive serology. In 2014, Ilus *et al*[61] conducted a retrospective investigation involving 32439 CeD patients in Finland, unveiling a positive link between CeD and SBC development. The study reported an SIR of 5 in females, 3.47 in males, and 4.29 in all combined cases. Another substantial retrospective Swedish study led by Emilsson *et al*[62], encompassing more than 48000 CeD patients, reported an HR of 3.05, underscoring the affirmative association between CeD and SBC. Additionally, a sequential progression from adenoma to carcinoma has been suggested as a potential pathway for SBC development in CeD[63]. Notably, the survival rates for SBC in CeD patients are comparatively higher than those in individuals without CeD[64]. As prostate cancer is the most common cancer in males in general[65], our study shows a positive association between prostate cancer and CeD with an HR of 1.14 (95%CI: 1.06-1.23). Surprisingly, other studies that addressed this association did not show any significantly heightened risk of prostate cancer in CeD[25,31,61,66].

To our knowledge, this study stands as one of the most extensive investigations underscoring the positive link between nonmelanoma skin cancers and CeD. In contrast, the association between melanoma and CeD has been examined in three studies, with one study, also conducted in the United States, reporting a notably elevated SIR[23]. Conversely, two studies from Sweden failed to establish any significant connection between these two conditions[31,67]. Notably, the latter study, which involved 29028 patients, did not identify a significant association.

Our study reveals a positive correlation between pancreatic malignancies and CeD. However, it's essential to note the divergence in findings across various studies concerning the association between CeD and pancreatic malignancies. For instance, Elfström *et al*[60] reported a substantially higher HR of 10.7 within the first year of follow-up, which subsequently decreased to 1.4. Lebwohl *et al*[26] conducted another large Swedish study, documented analogous outcomes with distinct HR. In contrast, a study utilizing a United States Veterans Affairs database reported an elevated RR for pancreatic cancer in individuals with CeD[68], while two separate European studies failed to identify any significant risk association[31,69].

Our results indicate an elevated incidence and a positive correlation between thyroid malignancies and CeD. It is worth mentioning that the existing literature has yielded conflicting outcomes in this regard. Specifically, two studies conducted in the United States and Italy have reported a positive association[70,71], whereas two other population-based studies in Sweden have reported a lack of significant association[31,72].

It is noteworthy that our study's findings align with those of other research regarding the risk of lung cancer in CeD patients. Our study reveals a statistically significant negative correlation between respiratory malignancies and CeD. Similarly, the two largest studies conducted in Finland[61] and Sweden[26] also report a negative association. Conversely, several other studies have failed to identify a heightened risk of lung malignancies in individuals with CeD[23-25,31,69,73,74]. This lack of association could potentially be attributed to a lower prevalence of smoking among individuals with CeD[75,76]. Regarding colorectal cancer, our study demonstrates no significant association with CeD. This finding is consistent with a study by Lebwohl *et al*[77], which also reported no elevated risk of colorectal cancer. However, results from the study by Ilus *et al*[61], indicated an increased risk of colon cancer but not rectal cancer.

In the context of breast cancer risk in CeD, most available studies have reported a significantly decreased risk, including large-scale investigations by Lebwohl *et al*[26], Ilus *et al*[61], and Ludvigsson *et al*[78], as well as other relatively smaller studies with similar findings[31,25,69,79]. Our study supports this trend, reporting no increased risk of breast cancer in individuals with CeD, which aligns with several previous studies on this association[23,24,73,74,80].

Strengths and limitations

Our study exhibits several notable strengths. First and foremost, it leverages an extensive database, including more than 108000 individuals diagnosed with CeD, which, when weighted, expands to encompass over 500000 individuals. This dataset stands as the most substantial cohort among comparable studies within the existing body of research, as far as our knowledge extends. Secondly, we investigated hospital outcomes, encompassing a variety of factors associated with mortality, LOS, and the burden on the healthcare system, spanning a substantial two-decade period. However, it is important to acknowledge several limitations in our study. Firstly, it is confined to inpatient populations, potentially limiting the generalizability of our findings to outpatient settings. Secondly, the NIS dataset lacks essential clinical details such as laboratory values, treatment modalities, and diagnostic procedures like histology and endoscopy findings that definitively confirm CeD. Thirdly, the NIS, as an administrative database, may be susceptible to selection bias and coding errors, which can occur without external validation. Lastly, it's worth noting that the NIS does not track individual patients, meaning that if a patient is admitted multiple times, they may contribute to multiple entries in the database. Furthermore, we lack information about the level of adherence to a gluten-free diet among the patients and the degree to which their CeD is controlled. These limitations should be considered when interpreting our results.

CONCLUSION

Our study is unique in highlighting the detailed results of positive, negative, or null associations between different hematologic and solid malignancies and CeD. It also sheds light on data on hospitalized CeD patients with and without MN in terms of mortality, LOS, and related costs with trends shown over the last two decades, which have been understudied in this disease.

FOOTNOTES

Author contributions: Haider MB and Green P designed the research study; Haider MB performed the data collection, analysis, and interpretation of results; Haider MB, Al Sbihi A, and Reddy SN wrote the manuscript; Green P supervised the project; and all authors have read and approved the final manuscript.

Institutional review board statement: Information from this research utilized de-identified data sourced from the National Inpatient Sample Database, which is a publicly accessible database encompassing all-payer inpatient care information in the United States. There is no necessity for an Institutional Review Board Approval Form or Document.

Informed consent statement: The study utilized de-identified data from the National Inpatient Sample Database, which is a publicly accessible database containing information on all-payer inpatient care in the United States. Patient consent was not necessary for this analysis.

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REFERENCES

1 **Lebwohl B**, Sanders DS, Green PHR. Coeliac disease. *Lancet* 2018; **391**: 70-81 [PMID: 28760445 DOI: 10.1016/S0140-6736(17)31796-8]
2 **Singh P**, Arora A, Strand TA, Leffler DA, Catassi C, Green PH, Kelly CP, Ahuja V, Makharia GK. Global Prevalence of Celiac Disease: Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2018; **16**: 823-836.e2 [PMID: 29551598 DOI: 10.1016/j.cgh.2017.06.037]

3 **Kagnoff MF**. Overview and pathogenesis of celiac disease. *Gastroenterology* 2005; **128**: S10-S18 [PMID: 15825116 DOI: 10.1053/j.gastro.2005.02.008]

4 **Parzanese I**, Qehajaj D, Patrinicola F, Aralica M, Chiriva-Internati M, Stifter S, Elli L, Grizzi F. Celiac disease: From pathophysiology to treatment. *World J Gastrointest Pathophysiol* 2017; **8**: 27-38 [PMID: 28573065 DOI: 10.4291/wjgp.v8.i2.27]

5 **Denham JM**, Hill ID. Celiac disease and autoimmunity: review and controversies. *Curr Allergy Asthma Rep* 2013; **13**: 347-353 [PMID: 23681421 DOI: 10.1007/s11882-013-0352-1]

6 **Pelizzaro F**, Marsilio I, Fassan M, Piazza F, Barberio B, D'Odorico A, Savarino EV, Farinati F, Zingone F. The Risk of Malignancies in Celiac Disease-A Literature Review. *Cancers (Basel)* 2021; **13** [PMID: 34771450 DOI: 10.3390/cancers13215288]

7 **Al-Toma A**, Volta U, Auricchio R, Castillejo G, Sanders DS, Cellier C, Mulder CJ, Lundin KEA. European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. *United European Gastroenterol J* 2019; **7**: 583-613 [PMID: 31210940 DOI: 10.1177/2050640619844125]

8 **Holmes GK**, Prior P, Lane MR, Pope D, Allan RN. Malignancy in coeliac disease--effect of a gluten free diet. *Gut* 1989; **30**: 333-338 [PMID: 2707633 DOI: 10.1136/gut.30.3.333]

9 **Collin P**, Reunala T, Pukkala E, Laippala P, Keyriläinen O, Pasternack A. Coeliac disease--associated disorders and survival. *Gut* 1994; **35**: 1215-1218 [PMID: 7959226 DOI: 10.1136/gut.35.9.1215]

10 **Rostami Nejad M**, Aldulaimi D, Ishaq S, Ehsani-Ardakani MJ, Zali MR, Malekzadeh R, Rostami K. Geographic trends and risk of gastrointestinal cancer among patients with celiac disease in Europe and Asian-Pacific region. *Gastroenterol Hepatol Bed Bench* 2013; **6**: 170-177 [PMID: 24834268]

11 **Agency for Healthcare Research and Quality**. NIS overview. [cited 12 December 2023]. Available from: https://www.hcup-us.ahrq.gov/nisoverview.jsp

12 **Agency for Healthcare Research and Quality**. Introduction to the HCUP National Inpatient Sample (NIS), 2015. [cited 12 October 2023]. Available from: www.hcup-us.ahrq.gov/db/nation/nis/NIS_Introduction_2015.jsp

13 **Agency for Healthcare Research and Quality**. DUA Training - Accessible Version. [cited 12 October 2023]. Available from: https://www.hcup-us.ahrq.gov/DUA/dua_508/DUA508version.jsp

14 **Agency for Healthcare Research and Quality**. US Bureau of Labor Statistics. [cited 10 March 2023]. Available from: https://data.bls.gov/timeseries/CUUR0000SA0

15 **Agency for Healthcare Research and Quality**. Trend weights for HCUP NIS data. [cited 15 December 2023]. Available from: https://www.hcup-us.ahrq.gov/db/nation/nis/trendwghts.jsp

16 **Kissel P**, Rauber G, Barrucand D, Marchal C, Leclère J. [Adenocarcinoma of the small intestine in the evolution of a celiac disease in an adult]. *Arch Mal Appar Dig Mal Nutr* 1965; **54**: 945-951 [PMID: 5853831]

17 **Austad WI**, Cornes JS, Gough KR, McCarthy CF, Read AE. Steatorrhea and malignant lymphoma. The relationship of malignant tumors of lymphoid tissue and celiac disease. *Am J Dig Dis* 1967; **12**: 475-490 [PMID: 6026426 DOI: 10.1007/BF02233180]

18 **Harris OD**, Cooke WT, Thompson H, Waterhouse JA. Malignancy in adult coeliac disease and idiopathic steatorrhoea. *Am J Med* 1967; **42**: 899-912 [PMID: 5338480 DOI: 10.1016/0002-9343(67)90071-x]

19 **Asquith P**. Adult coeliac disease and malignancy. *Ir Med J* 1974; **67**: 417-420 [PMID: 4411887]

20 **Evans IM**. Coeliac disease and malignancy. *Br Med J* 1977; **2**: 1026-1027 [PMID: 922375 DOI: 10.1136/bmj.2.6093.1026-d]

21 **Cooper BT**, Holmes GK, Ferguson R, Cooke WT. Celiac disease and malignancy. *Medicine (Baltimore)* 1980; **59**: 249-261 [PMID: 7392945 DOI: 10.1097/00005792-198007000-00002]

22 **Swinson CM**, Slavin G, Coles EC, Booth CC. Coeliac disease and malignancy. *Lancet* 1983; **1**: 111-115 [PMID: 6129425 DOI: 10.1016/s0140-6736(83)91754-3]

23 **Green PH**, Fleischauer AT, Bhagat G, Goyal R, Jabri B, Neugut AI. Risk of malignancy in patients with celiac disease. *Am J Med* 2003; **115**: 191-195 [PMID: 12935825 DOI: 10.1016/s0002-9343(03)00302-4]

24 **Card TR**, West J, Holmes GK. Risk of malignancy in diagnosed coeliac disease: a 24-year prospective, population-based, cohort study. *Aliment Pharmacol Ther* 2004; **20**: 769-775 [PMID: 15379837 DOI: 10.1111/j.1365-2036.2004.02177.x]

25 **West J**, Logan RF, Smith CJ, Hubbard RB, Card TR. Malignancy and mortality in people with coeliac disease: population based cohort study. *BMJ* 2004; **329**: 716-719 [PMID: 15269095 DOI: 10.1136/bmj.38169.486701.7C]

26 **Lebwohl B**, Green PHR, Emilsson L, Mårild K, Söderling J, Roelstraete B, Ludvigsson JF. Cancer Risk in 47,241 Individuals With Celiac Disease: A Nationwide Cohort Study. *Clin Gastroenterol Hepatol* 2022; **20**: e111-e131 [PMID: 34033925 DOI: 10.1016/j.cgh.2021.05.034]

27 **Grainge MJ**, West J, Card TR, Holmes GK. Causes of death in people with celiac disease spanning the pre- and post-serology era: a population-based cohort study from Derby, UK. *Am J Gastroenterol* 2011; **106**: 933-939 [PMID: 21245833 DOI: 10.1038/ajg.2010.506]

28 **Cottone M**, Termini A, Oliva L, Magliocco A, Marrone C, Orlando A, Pinzone F, Di Mitri R, Rosselli M, Rizzo A, Pagliaro L. Mortality and causes of death in celiac disease in a Mediterranean area. *Dig Dis Sci* 1999; **44**: 2538-2541 [PMID: 10630509 DOI: 10.1023/a:1026655609906]

29 **Corrao G**, Corazza GR, Bagnardi V, Brusco G, Ciacci C, Cottone M, Sategna Guidetti C, Usai P, Cesari P, Pelli MA, Loperfido S, Volta U, Calabró A, Certo M; Club del Tenue Study Group. Mortality in patients with coeliac disease and their relatives: a cohort study. *Lancet* 2001; **358**: 356-361 [PMID: 11502314 DOI: 10.1016/s0140-6736(01)05554-4]

30 **Peters U**, Askling J, Gridley G, Ekbom A, Linet M. Causes of death in patients with celiac disease in a population-based Swedish cohort. *Arch Intern Med* 2003; **163**: 1566-1572 [PMID: 12860579 DOI: 10.1001/archinte.163.13.1566]

31 **Askling J**, Linet M, Gridley G, Halstensen TS, Ekström K, Ekbom A. Cancer incidence in a population-based cohort of individuals hospitalized with celiac disease or dermatitis herpetiformis. *Gastroenterology* 2002; **123**: 1428-1435 [PMID: 12404215 DOI: 10.1053/gast.2002.36585]

32 **Dunne MR**, Byrne G, Chirdo FG, Feighery C. Coeliac Disease Pathogenesis: The Uncertainties of a Well-Known Immune Mediated Disorder. *Front Immunol* 2020; **11**: 1374 [PMID: 32733456 DOI: 10.3389/fimmu.2020.01374]

33 **Green PH**, Jabri B. Celiac disease and other precursors to small-bowel malignancy. *Gastroenterol Clin North Am* 2002; **31**: 625-639 [PMID: 12134621 DOI: 10.1016/s0889-8553(02)00010-9]

34 **Gale J**, Simmonds PD, Mead GM, Sweetenham JW, Wright DH. Enteropathy-type intestinal T-cell lymphoma: clinical features and treatment of 31 patients in a single center. *J Clin Oncol* 2000; **18**: 795-803 [PMID: 10673521 DOI: 10.1200/JCO.2000.18.4.795]

35 **Egan LJ**, Walsh SV, Stevens FM, Connolly CE, Egan EL, McCarthy CF. Celiac-associated lymphoma. A single institution experience of 30 cases in the combination chemotherapy era. *J Clin Gastroenterol* 1995; **21**: 123-129 [PMID: 8583077]

36 **Nielsen OH**, Jacobsen O, Pedersen ER, Rasmussen SN, Petri M, Laulund S, Jarnum S. Non-tropical sprue. Malignant diseases and mortality rate. *Scand J Gastroenterol* 1985; **20**: 13-18 [PMID: 3992161 DOI: 10.3109/00365528509089626]

37 **Catassi C**, Fabiani E, Corrao G, Barbato M, De Renzo A, Carella AM, Gabrielli A, Leoni P, Carroccio A, Baldassarre M, Bertolani P, Caramaschi P, Sozzi M, Guariso G, Volta U, Corazza GR; Italian Working Group on Coeliac Disease and Non-Hodgkin's-Lymphoma. Risk of non-Hodgkin lymphoma in celiac disease. *JAMA* 2002; **287**: 1413-1419 [PMID: 11903028 DOI: 10.1001/jama.287.11.1413]

38 **Smedby KE**, Akerman M, Hildebrand H, Glimelius B, Ekbom A, Askling J. Malignant lymphomas in coeliac disease: evidence of increased risks for lymphoma types other than enteropathy-type T cell lymphoma. *Gut* 2005; **54**: 54-59 [PMID: 15591504 DOI: 10.1136/gut.2003.032094]

39 **Elfström P**, Granath F, Ekström Smedby K, Montgomery SM, Askling J, Ekbom A, Ludvigsson JF. Risk of lymphoproliferative malignancy in relation to small intestinal histopathology among patients with celiac disease. *J Natl Cancer Inst* 2011; **103**: 436-444 [PMID: 21289299 DOI: 10.1093/jnci/djq564]

40 **Leonard JN**, Tucker WF, Fry JS, Coulter CA, Boylston AW, McMinn RM, Haffenden GP, Swain AF, Fry L. Increased incidence of malignancy in dermatitis herpetiformis. *Br Med J (Clin Res Ed)* 1983; **286**: 16-18 [PMID: 6401441 DOI: 10.1136/bmj.286.6358.16]

41 **Sigurgeirsson B**, Agnarsson BA, Lindelöf B. Risk of lymphoma in patients with dermatitis herpetiformis. *BMJ* 1994; **308**: 13-15 [PMID: 8298344 DOI: 10.1136/bmj.308.6920.13]

42 **Sharaiha RZ**, Lebwohl B, Reimers L, Bhagat G, Green PH, Neugut AI. Increasing incidence of enteropathy-associated T-cell lymphoma in the United States, 1973-2008. *Cancer* 2012; **118**: 3786-3792 [PMID: 22169928 DOI: 10.1002/cncr.26700]

43 **Catassi C**, Kryszak D, Bhatti B, Sturgeon C, Helzlsouer K, Clipp SL, Gelfond D, Puppa E, Sferruzza A, Fasano A. Natural history of celiac disease autoimmunity in a USA cohort followed since 1974. *Ann Med* 2010; **42**: 530-538 [PMID: 20868314 DOI: 10.3109/07853890.2010.514285]

44 **Rubio-Tapia A**, Kyle RA, Kaplan EL, Johnson DR, Page W, Erdtmann F, Brantner TL, Kim WR, Phelps TK, Lahr BD, Zinsmeister AR, Melton LJ 3rd, Murray JA. Increased prevalence and mortality in undiagnosed celiac disease. *Gastroenterology* 2009; **137**: 88-93 [PMID: 19362553 DOI: 10.1053/j.gastro.2009.03.059]

45 **Cellier C**, Delabesse E, Helmer C, Patey N, Matuchansky C, Jabri B, Macintyre E, Cerf-Bensussan N, Brousse N. Refractory sprue, coeliac disease, and enteropathy-associated T-cell lymphoma. French Coeliac Disease Study Group. *Lancet* 2000; **356**: 203-208 [PMID: 10963198 DOI: 10.1016/s0140-6736(00)02481-8]

46 **Rubio-Tapia A**, Murray JA. Classification and management of refractory coeliac disease. *Gut* 2010; **59**: 547-557 [PMID: 20332526 DOI: 10.1136/gut.2009.195131]

47 **Delabie J**, Holte H, Vose JM, Ullrich F, Jaffe ES, Savage KJ, Connors JM, Rimsza L, Harris NL, Müller-Hermelink K, Rüdiger T, Coiffier B, Gascoyne RD, Berger F, Tobinai K, Au WY, Liang R, Montserrat E, Hochberg EP, Pileri S, Federico M, Nathwani B, Armitage JO, Weisenburger DD. Enteropathy-associated T-cell lymphoma: clinical and histological findings from the international peripheral T-cell lymphoma project. *Blood* 2011; **118**: 148-155 [PMID: 21566094 DOI: 10.1182/blood-2011-02-335216]

48 **Chott A**, Haedicke W, Mosberger I, Födinger M, Winkler K, Mannhalter C, Müller-Hermelink HK. Most CD56+ intestinal lymphomas are CD8+CD5-T-cell lymphomas of monomorphic small to medium size histology. *Am J Pathol* 1998; **153**: 1483-1490 [PMID: 9811340 DOI: 10.1016/S0002-9440(10)65736-7]

49 **Tse E**, Gill H, Loong F, Kim SJ, Ng SB, Tang T, Ko YH, Chng WJ, Lim ST, Kim WS, Kwong YL. Type II enteropathy-associated T-cell lymphoma: a multicenter analysis from the Asia Lymphoma Study Group. *Am J Hematol* 2012; **87**: 663-668 [PMID: 22641357 DOI: 10.1002/ajh.23213]

50 **Deleeuw RJ**, Zettl A, Klinker E, Haralambieva E, Trottier M, Chari R, Ge Y, Gascoyne RD, Chott A, Müller-Hermelink HK, Lam WL. Whole-genome analysis and HLA genotyping of enteropathy-type T-cell lymphoma reveals 2 distinct lymphoma subtypes. *Gastroenterology* 2007; **132**: 1902-1911 [PMID: 17484883 DOI: 10.1053/j.gastro.2007.03.036]

51 **Nelson R**. Celiac Disease and Lymphoma: What's the Connection? [cited 10 June 2024]. Available from: https://www.patientpower.info/lymphoma/celiac-disease-and-lymphoma

52 **Lebwohl B**. Celiac Disease and Lymphoma: Researcher Explains the Risk. [cited 10 June 2024]. Available from: https://www.beyondceliac.org/research-news/celiac-disease-and-lymphoma-researcher-explains-the-risk/

53 **Di Sabatino A**, Biagi F, Gobbi PG, Corazza GR. How I treat enteropathy-associated T-cell lymphoma. *Blood* 2012; **119**: 2458-2468 [PMID: 22271451 DOI: 10.1182/blood-2011-10-385559]

54 **Smedby KE**, Hjalgrim H, Askling J, Chang ET, Gregersen H, Porwit-MacDonald A, Sundström C, Akerman M, Melbye M, Glimelius B, Adami HO. Autoimmune and chronic inflammatory disorders and risk of non-Hodgkin lymphoma by subtype. *J Natl Cancer Inst* 2006; **98**: 51-60 [PMID: 16391371 DOI: 10.1093/jnci/djj004]

55 **Ansell P**, Simpson J, Lightfoot T, Smith A, Kane E, Howell D, Newton R, McGonagle D, Jack A, Roman E. Non-Hodgkin lymphoma and autoimmunity: does gender matter? *Int J Cancer* 2011; **129**: 460-466 [PMID: 20853323 DOI: 10.1002/ijc.25680]

56 **Leslie LA**, Lebwohl B, Neugut AI, Gregory Mears J, Bhagat G, Green PH. Incidence of lymphoproliferative disorders in patients with celiac disease. *Am J Hematol* 2012; **87**: 754-759 [PMID: 22641457 DOI: 10.1002/ajh.23237]

57 **Abdul Sultan A**, Crooks CJ, Card T, Tata LJ, Fleming KM, West J. Causes of death in people with coeliac disease in England compared with the general population: a competing risk analysis. *Gut* 2015; **64**: 1220-1226 [PMID: 25344479 DOI: 10.1136/gutjnl-2014-308285]

58 **Halfdanarson TR**, Rubio-Tapia A, Ristow KM, Habermann TM, Murray JA, Inwards DJ. Patients with celiac disease and B-cell lymphoma have a better prognosis than those with T-cell lymphoma. *Clin Gastroenterol Hepatol* 2010; **8**: 1042-1047 [PMID: 20851210 DOI: 10.1016/j.cgh.2010.09.007]

59 **Daum S**, Ullrich R, Heise W, Dederke B, Foss HD, Stein H, Thiel E, Zeitz M, Riecken EO. Intestinal non-Hodgkin's lymphoma: a multicenter prospective clinical study from the German Study Group on Intestinal non-Hodgkin's Lymphoma. *J Clin Oncol* 2003; **21**: 2740-2746 [PMID: 12860953 DOI: 10.1200/JCO.2003.06.026]

60 **Elfström P**, Granath F, Ye W, Ludvigsson JF. Low risk of gastrointestinal cancer among patients with celiac disease, inflammation, or latent celiac disease. *Clin Gastroenterol Hepatol* 2012; **10**: 30-36 [PMID: 21723236 DOI: 10.1016/j.cgh.2011.06.029]

61 **Ilus T**, Kaukinen K, Virta LJ, Pukkala E, Collin P. Incidence of malignancies in diagnosed celiac patients: a population-based estimate. *Am J Gastroenterol* 2014; **109**: 1471-1477 [PMID: 25047399 DOI: 10.1038/ajg.2014.194]

62 **Emilsson L**, Semrad C, Lebwohl B, Green PHR, Ludvigsson JF. Risk of Small Bowel Adenocarcinoma, Adenomas, and Carcinoids in a Nationwide Cohort of Individuals With Celiac Disease. *Gastroenterology* 2020; **159**: 1686-1694.e2 [PMID: 32679218 DOI: 10.1053/j.gastro.2020.07.007]

63 **Rampertab SD**, Forde KA, Green PH. Small bowel neoplasia in coeliac disease. *Gut* 2003; **52**: 1211-1214 [PMID: 12865284 DOI: 10.1136/gut.52.8.1211]

64 **Potter DD**, Murray JA, Donohue JH, Burgart LJ, Nagorney DM, van Heerden JA, Plevak MF, Zinsmeister AR, Thibodeau SN. The role of defective mismatch repair in small bowel adenocarcinoma in celiac disease. *Cancer Res* 2004; **64**: 7073-7077 [PMID: 15466202 DOI: 10.1158/0008-5472.CAN-04-1096]

65 **Leslie SW**, Soon-Sutton TL, R I A, Sajjad H, Skelton WP. Prostate Cancer. 2023 Nov 13. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan- [PMID: 29261872]

66 **Ludvigsson JF**, Fall K, Montgomery S. Risk of prostate cancer in a population-based cohort of men with coeliac disease. *Br J Cancer* 2012; **106**: 217-221 [PMID: 22134505 DOI: 10.1038/bjc.2011.536]

67 **Lebwohl B**, Eriksson H, Hansson J, Green PH, Ludvigsson JF. Risk of cutaneous malignant melanoma in patients with celiac disease: a population-based study. *J Am Acad Dermatol* 2014; **71**: 245-248 [PMID: 24792481 DOI: 10.1016/j.jaad.2014.03.029]

68 **Landgren AM**, Landgren O, Gridley G, Dores GM, Linet MS, Morton LM. Autoimmune disease and subsequent risk of developing alimentary tract cancers among 4.5 million US male veterans. *Cancer* 2011; **117**: 1163-1171 [PMID: 21381009 DOI: 10.1002/cncr.25524]

69 **Goldacre MJ**, Wotton CJ, Yeates D, Seagroatt V, Jewell D. Cancer in patients with ulcerative colitis, Crohn's disease and coeliac disease: record linkage study. *Eur J Gastroenterol Hepatol* 2008; **20**: 297-304 [PMID: 18334873 DOI: 10.1097/MEG.0b013e3282f2a5e2]

70 **Kent L**, McBride R, McConnell R, Neugut AI, Bhagat G, Green PH. Increased risk of papillary thyroid cancer in celiac disease. *Dig Dis Sci* 2006; **51**: 1875-1877 [PMID: 16957996 DOI: 10.1007/s10620-006-9240-z]

71 **Volta U**, Vincentini O, Silano M; Collaborating Centers of the Italian Registry of Celiac Disease. Papillary cancer of thyroid in celiac disease. *J Clin Gastroenterol* 2011; **45**: e44-e46 [PMID: 20697293 DOI: 10.1097/MCG.0b013e3181ea11cb]

72 **Ludvigsson JF**, Lebwohl B, Kämpe O, Murray JA, Green PH, Ekbom A. Risk of thyroid cancer in a nationwide cohort of patients with biopsy-verified celiac disease. *Thyroid* 2013; **23**: 971-976 [PMID: 23281890 DOI: 10.1089/thy.2012.0306]

73 **Grainge MJ**, West J, Solaymani-Dodaran M, Card TR, Logan RF. The long-term risk of malignancy following a diagnosis of coeliac disease or dermatitis herpetiformis: a cohort study. *Aliment Pharmacol Ther* 2012; **35**: 730-739 [PMID: 22288441 DOI: 10.1111/j.1365-2036.2012.04998.x]

74 **Viljamaa M**, Kaukinen K, Pukkala E, Hervonen K, Reunala T, Collin P. Malignancies and mortality in patients with coeliac disease and dermatitis herpetiformis: 30-year population-based study. *Dig Liver Dis* 2006; **38**: 374-380 [PMID: 16627018 DOI: 10.1016/j.dld.2006.03.002]

75 **Vazquez H**, Smecuol E, Flores D, Mazure R, Pedreira S, Niveloni S, Mauriño E, Bai JC. Relation between cigarette smoking and celiac disease: evidence from a case-control study. *Am J Gastroenterol* 2001; **96**: 798-802 [PMID: 11280554 DOI: 10.1111/j.1572-0241.2001.03625.x]

76 **Suman S**, Williams EJ, Thomas PW, Surgenor SL, Snook JA. Is the risk of adult coeliac disease causally related to cigarette exposure? *Eur J Gastroenterol Hepatol* 2003; **15**: 995-1000 [PMID: 12923372 DOI: 10.1097/00042737-200309000-00009]

77 **Lebwohl B**, Stavsky E, Neugut AI, Green PH. Risk of colorectal adenomas in patients with coeliac disease. *Aliment Pharmacol Ther* 2010; **32**: 1037-1043 [PMID: 20937050 DOI: 10.1111/j.1365-2036.2010.04440.x]

78 **Ludvigsson JF**, West J, Ekbom A, Stephansson O. Reduced risk of breast, endometrial and ovarian cancer in women with celiac disease. *Int J Cancer* 2012; **131**: E244-E250 [PMID: 21953605 DOI: 10.1002/ijc.26454]

79 **Silano M**, Volta U, Mecchia AM, Dessì M, Di Benedetto R, De Vincenzi M; Collaborating centers of the Italian registry of the complications of coeliac disease. Delayed diagnosis of coeliac disease increases cancer risk. *BMC Gastroenterol* 2007; **7**: 8 [PMID: 17349035 DOI: 10.1186/1471-230X-7-8]

80 **Lohi S**, Mäki M, Montonen J, Knekt P, Pukkala E, Reunanen A, Kaukinen K. Malignancies in cases with screening-identified evidence of coeliac disease: a long-term population-based cohort study. *Gut* 2009; **58**: 643-647 [PMID: 18852259 DOI: 10.1136/gut.2007.140970]

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