Published in final edited form as:
Cancer. 2011 March 15; 117(6): 1163–1171. doi:10.1002/cncr.25524.

Autoimmune disease and subsequent risk of developing alimentary tract cancers among 4.5 million U.S. male Veterans

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Abstract

Background—Autoimmunity is clearly linked with hematologic malignancies, but less is known about autoimmunity and alimentary tract cancer risk, despite the specific targeting of alimentary organs and tissues by several autoimmune diseases. We therefore conducted the first systematic evaluation of a broad range of specific autoimmune diseases and risk for subsequent alimentary tract cancer.

Methods—Based on 4,501,578 U.S. male Veterans, we identified 96,277 men who developed alimentary tract cancer during up to 26.2 years of follow-up. Using Poisson regression methods we calculated relative risks (RR) and 95% confidence intervals.

Results—A history of autoimmune disease with localized alimentary tract effects generally increased cancer risks in the organ(s) affected by the autoimmune disease, such as primary biliary cirrhosis and liver cancer (RR=6.01, 4.76–7.57); pernicious anemia and stomach cancer (RR=3.17, 2.47–4.07); and ulcerative colitis and small intestine, colon, and rectal cancers (RR=2.53, 1.05–6.11; RR=2.06, 1.70–2.48; and RR=2.07, 1.62–2.64, respectively). In addition, a history of celiac disease, reactive arthritis (Reiter's disease), localized scleroderma, and systemic sclerosis all were associated significantly with increased risk of esophageal cancer (RR=1.86–2.86). Autoimmune diseases without localized alimentary tract effects generally were not associated with alimentary tract cancer risk, with the exception of decreased risk for multiple alimentary tract cancers associated with a history of multiple sclerosis.

Conclusions—Our findings support the importance of localized inflammation in alimentary tract carcinogenesis. Future research is needed to confirm our findings and improve our understanding of underlying mechanisms by which autoimmune diseases contribute to alimentary tract carcinogenesis.

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Disclosures: No conflicts of interest or financial disclosures exist

Keywords

Alimentary; gastrointestinal; autoimmune disease; inflammation; cancer

INTRODUCTION

Autoimmunity is characterized by immune dysregulation and reactivity to self-antigens, resulting in damage to cells and tissues. Autoimmune diseases may have systemic involvement (e.g., rheumatoid arthritis (RA), which targets the joints, but may also affect other organs) or localized, organ-specific involvement (e.g., ulcerative colitis, which targets the lining of the colon and rectum). Although the pathophysiology of many autoimmune diseases is not well-understood, patients are commonly treated with various types of immune-modulatory drugs, such as steroids, cytotoxic agents, and non-steroidal anti-inflammatory drugs.[1]

Previous research on the association between autoimmune diseases and subsequent malignancy has particularly focused on the increased risk of developing lymphoid malignancies among patients with certain autoimmune diseases, such as RA, Sjögren's syndrome, systemic lupus erythematosus (SLE), and systemic sclerosis (SS).[2] Although several autoimmune diseases specifically target organs and tissues within the alimentary tract, such as ulcerative colitis and Crohn's disease (intestinal tract), primary biliary cirrhosis (PBC) (liver), and pernicious anemia (PA) (stomach), much less is currently known about autoimmunity and the risk of developing alimentary tract cancers. The limited literature linking autoimmunity with alimentary tract cancers includes relatively few autoimmune diseases, for example RA and decreased risk of colorectal cancer,3 and pernicious anemia and increased risks of buccal, pharynx, and stomach cancers.4–6

We conducted the first systematic evaluation of a broad range of defined autoimmune conditions in relation to the subsequent risk of developing alimentary tract cancers, using data derived from a large population-based study including over 4.5 million adult male Veterans admitted to United States (U.S.) Veterans Affairs (VA) hospitals.

METHODS

Study population, data collection, and patients

The study cohort was identified from inpatient records from 142 U.S. VA hospital admissions between July 1, 1969, and September 30, 1996. Based on U.S. census data, 30 million Veterans were entitled to admission to VA hospitals during the study period.[7] 4,501,578 African American and white male Veterans who were hospitalized between the ages of 18–100 and had no prior malignancy were eligible for the study and included in the final analytic cohort (Table 1). Due to small numbers, other ethnic/racial groups and females were not included. Since the study was based on analysis of existing data without personal identifiers, the National Institutes of Health Office of Human Subjects Research granted an exemption from Institutional Review Board review and waived the requirement for informed consent.

Ascertainment of autoimmune diseases and alimentary tract cancers

A total of 288,982 patients with specific autoimmune diseases were identified from discharge diagnoses as defined by the 8th and 9th revisions of the International Classification of Diseases (ICDA, ICD9-CM) (Table 2). The vast majority of these patients (89.9%) were diagnosed with a single autoimmune disease, 8.9% with two, and 1.2% with three or more

autoimmune diseases. The most commonly co-occurring autoimmune diagnoses were RA with ankylosing spondylitis, chronic rheumatic heart disease, or psoriasis; rheumatic fever with chronic rheumatic heart disease; SLE with discoid lupus erythematosus; and Crohn's disease with ulcerative colitis.

We grouped autoimmune diseases based on the presence or absence of alimentary tract involvement in that condition,[1,4–6,8–14] defined as likely having a localized effect at any site within the alimentary tract, ranging from substantial involvement (e.g., ulcerative colitis, Crohn's disease) to minimal clinically observed involvement (e.g., sarcoidosis). Patients who developed a first primary alimentary tract cancer were identified from discharge diagnoses as defined by ICDA or ICD9-CM codes (buccal: 140–149, esophagus: 150, stomach: 151, small intestine: 152, colon: 153, rectum/anus: 154, liver: 155, gallbladder: 156, pancreas: 157).

Statistical analysis

Patients were followed from one year after their index hospital discharge until the first discharge diagnosis of malignancy, death, or end of study (September 30, 1996), whichever occurred first. Dates of death were ascertained from record linkage to Social Security Administration mortality files. Latency was estimated by subtracting the date of discharge from the first hospitalization listing a diagnosis of an autoimmune disease from the date of admission for the first hospitalization listing a diagnosis of cancer. To minimize the influence of reverse causality, all analyses were restricted to individuals with their first hospital discharge with an autoimmune disease diagnosis at least 1 year prior to the first hospitalization listing a diagnosis of cancer.

Relative risks (RR) and 95% confidence intervals (CI) were estimated using Poisson regression,[15] comparing the site-specific cancer risks among men with a discharge diagnosis of a specific autoimmune disease to risks among men who did not have a discharge diagnosis of that specific disease. All risk estimates were adjusted for attained age (<40, 40–49, 50–59, 60–69, 70–79, ≥80 years) and calendar year (1969–1974, 1975–1979, 1980–1984, 1985–1989, 1990–1996), race (African American/ white), number of hospital visits (1–2, 3–4, ≥5), and time between study entry and exit (2–3, 4–5, 6–9, 10–14, ≥15 years). Additional potential confounding comorbid conditions were evaluated using discharge diagnoses (Table 3). Risk estimates for buccal, esophagus, and liver cancers were also adjusted for alcoholism because inclusion of this variable in the regression models resulted in a >10% change in the risk estimates for a number of autoimmune diseases and alimentary tract cancers. Additional adjustment for other potential confounders (Table 3) did not materially (>10%) change the risk estimates for any alimentary tract cancer site associated with any of the autoimmune diseases; these variables were therefore excluded from the final regression models (data not shown).

Due to the rarity of some autoimmune diseases and alimentary tract cancers, we present risk estimates for black and white males combined. P-values were two-sided and P-values <0.05 were considered statistically significant. Calculations were performed using AMFIT Poisson regression models (Epicure Version 2.0; HiroSoft International Corporation, Seattle, Washington).

RESULTS

In this study of 4,501,578 hospitalized male Veterans, we identified 96,277 men who developed an alimentary tract cancer during up to 26.2 years of follow-up (Table 1). Patients who developed an alimentary tract cancer tended to be older at first hospitalization and hospitalized more often than patients who did not develop a solid cancer.

Table 2 presents risks of alimentary tract cancers associated with specific autoimmune diseases and their diagnosis codes. Autoimmune diseases with at least some localized effects in the alimentary tract were generally associated with increased risk of alimentary tract cancers, although the patterns differed for specific autoimmune diseases. PA, PBC, and ulcerative colitis were associated with increased cancer risk in multiple sites within the alimentary tract, with the strongest risks observed for cancers in the same organs as the localized effects of the autoimmune diseases. For example, risk of liver cancer was 6-fold among patients with a history of PBC; risk of stomach cancer was 3-fold among patients with a history of PA; and risks of small intestine, colon, and rectal cancers were 2-fold among patients with a history of ulcerative colitis. Several other autoimmune diseases were associated with increased cancer risk at a single alimentary tract site. Most notably, a history of celiac disease, reactive arthritis, localized scleroderma, and SS all were associated significantly with increased risk of esophageal cancer (RR=1.86–2.86).

In contrast, autoimmune conditions without localized effects in the alimentary tract generally were not significantly associated with risk of alimentary tract cancers, with the exception of two notable patterns. First, a prior history of multiple sclerosis (MS) was associated significantly with decreased cancer risk in multiple alimentary tract sites, including decreased risks for cancers of the buccal cavity, esophagus, liver, and pancreas (RR=0.42–0.62). Decreased risk of buccal cavity cancer also was associated significantly with a prior history of ankylosing spondylitis, chronic rheumatic heart disease, Graves' disease, and RA (RR=0.55–0.84).

Observed risk estimates were generally very similar when we excluded cancers diagnosed within 5 years of autoimmune disease diagnosis (data not shown). Observed risk estimates for colon cancer were also very similar when we conducted analyses excluding patients who had total colectomy before inclusion or during follow-up and thus were not at risk for colon cancer (N=69; data not shown).

DISCUSSION

Here we present the first large exploratory investigation of a wide range of specific autoimmune diseases and subsequent risks for alimentary tract cancers. We found that a prior history of certain autoimmune conditions with known alimentary tract involvement (e.g., ulcerative colitis and PBC) were associated with increased risks of developing alimentary tract cancers. Other autoimmune diseases generally were not associated with alimentary tract cancers, although MS was associated with decreased risks of cancers of the buccal cavity, esophagus, liver, and pancreas. These findings broadly support the potential importance of localized inflammation, characterized by release of various factors that promote cell proliferation, oxidative DNA damage, and other related features, in alimentary tract carcinogenesis.[16–18] The complexity of the observed patterns stresses the need for future studies designed to uncover underlying mechanisms between specific autoimmune diseases and alimentary tract cancers, and to improve our understanding of immune modulation, chronic immune stimulation, and inflammation in carcinogenesis.

Among autoimmune diseases with at least some localized effects in the alimentary tract organs, we generally observed the strongest increased risks for cancers in those sites. For example, we observed 3-fold risk of stomach cancer among patients with PA, which is consistent with previous reports,[4–6]. The main consequence of PA is vitamin B12 deficiency and chronic inflammation of the gastric mucosa, supporting the importance of localized inflammation in stomach carcinogenesis.[19–22] The observed association between stomach cancer and PBC, although consistent with a previous study and case report,[23,24] was unexpected because the effects of PBC are thought to be highly specific to the bile ducts.[25]

Liver cancer risk was increased strikingly among patients with a history of PBC. PBC is characterized by the presence of anti-mitochondrial antibodies and T-lymphocyte-mediated destruction of biliary epithelial cells, ultimately leading to cirrhosis.[25] The observed association is consistent with the general knowledge that chronic hepatitis or cirrhosis of any cause is associated with increased liver cancer risk,[26] as well as previous investigations of PBC and liver cancer risk.[23]

Liver cancer was also strongly associated with immune thrombocytopenic purpura (ITP). Primary ITP is a clinical diagnosis that is based on the exclusion of other initiating and/or underlying causes of thrombocytopenia.[27] Secondary ITP can be associated with a number of causes such as alcohol use, viral infections (including hepatitis C, Epstein-Barr, and others) and lymphoproliferative diseases, some of which may also be related to liver cancer risk. 27,28 We present liver cancer risk estimates adjusted for alcoholism, and additional adjustment for hepatitis did not materially change the risk estimates. Nevertheless, our finding of an association between ITP and liver cancer may reflect our inability to differentiate primary from secondary ITP, and it is likely that this disease category included both. We also observed modestly increased liver cancer risk among patients with a history of ulcerative colitis. This association has been reported previously, although the mechanism is uncertain.29–31

Pancreatic cancer risk was significantly associated with celiac disease and PBC. Patients with celiac disease have chronic inflammation of the small intestinal mucosa. Pancreatitis, impaired exocrine pancreatic function, malnutrition, and resulting pancreatic atrophy have been documented among patients with celiac disease,[32,33] which may predispose patients with celiac disease to pancreatic cancer. However, previous investigations of the association between celiac disease and pancreatic cancer are conflicting, possibly due to small sample sizes.[30,34] It is also possible that the observed association between celiac disease and pancreatic cancer reflects the co-existence of other undetected autoimmune phenomena that affect pancreatic cancer risk, because other autoantibodies, including those that target the pancreas, have also been documented among patients with celiac disease.[35] Similar to stomach cancer, our finding of an association between PBC and pancreatic cancer, although consistent with Goldacre et al.,[23] was unexpected because the effects of PBC are thought to be highly specific to the bile ducts.[25]

We observed that esophageal cancer risk was increased among patients with a history of celiac disease, ITP, reactive arthritis, localized scleroderma, and systemic sclerosis. Esophageal dysmotility, chronic gastroesophageal reflux, and subsequent chronic esophagitis are well documented in SS and celiac disease, and to a lesser extent in localized scleroderma as it becomes more diffuse. It is plausible that these changes increase risk for esophageal cancer, and previous literature supports associations between these autoimmune conditions and esophageal cancer.[30,34,36–38] The observed associations between esophageal cancer and ITP and reactive arthritis have not been reported previously. Although it is plausible that ITP increases risk of esophageal cancer because of mucosal bleeding and resultant tissue damage, the association may reflect the inclusion of both, primary and secondary ITP, in this disease category. The association with reactive arthritis was unexpected because the esophagus is not a typical extra-articular site of involvement.

The relationship between colorectal cancer risk and inflammatory bowel diseases is well-established.[39] Among patients with ulcerative colitis, we observed 2-fold risk of small intestine, colon, and rectal cancers, which is consistent with previous literature.[30,31] Among patients with Crohn's disease, we observed strikingly high 8-fold risk of small intestinal cancer, borderline increased risk of colon cancer, and no association with rectal cancer, which is also consistent with previous literature, although some previous studies have found

strong associations between colon cancer risk and Crohn's disease.[39–44] Several previous studies have reported decreased colorectal cancer risk among patients with RA,[3,45–47] which is consistent with our findings, although our estimated relative risks only reached borderline statistical significance.

Unexpectedly, we observed that buccal cancer risk was increased among patients with a history of discoid lupus erythematosus, ITP, PA, and PBC, and decreased among patients with a history of ankylosing spondylitis, chronic rheumatic heart disease, Graves' disease, and RA. The known risk factors for buccal cancers include tobacco, alcohol, viral infections, and diet.[48] We present risk estimates for buccal cancer adjusted for alcoholism, but the inclusion of smoking-related diagnoses and HIV infection did not materially alter the risk estimates. Although the main risk factors for buccal cancer all are thought to act via direct oncogenic effects rather than an immune-mediated mechanism, further research is needed to confirm our findings and explore the possible underlying mechanisms because only the association between buccal cancer and PA has been reported previously.[4–6] Given that buccal cancer includes several primary sites, some with differing risk factors, it is plausible that specific autoimmune diseases may be associated with different types of buccal cancer, but we did not have sufficient power to examine this hypothesis.

Decreased cancer risks have been observed in patients with MS, particularly in untreated patients, although few studies have comprehensively assessed site-specific risks within the digestive tract.[49–52] Consistent with these reports, we found that patients with MS had significantly decreased risk for several alimentary tract cancers, including buccal, esophageal, liver, and pancreatic cancers, and borderline decreased risk for rectal cancer. It has been postulated that the innate immune profile of patients with MS, characterized by increased T helper 1 (Th1)-type immune activation and correspondingly altered cytokine levels, may inhibit (or protect from) carcinogenesis.[53–57] Notably, with the introduction of immunomodulatory agents for the treatment of MS in the early 1990s, cancer risk may change in the future due to effects of these therapies, as has been observed for breast cancer in this population.[49,50] Finally, the possibility remains that the inverse association between MS and various cancers may reflect decreased medical surveillance in a potentially severely debilitated hospitalized population. Additional research to further investigate the reduced risk of cancer overall among MS patients is warranted.

Several strengths and limitations should be considered in the interpretation of our results. Our large study population included socioeconomically diverse patients with relatively stable access to medical care and with long-term follow-up. Clinical diagnoses were obtained from medical records and thus were not subject to recall bias. Limitations include the lack of detailed clinical information on autoimmune diseases, including diagnostic testing and treatment, and other potential cancer risk-factors (e.g., physical activity, BMI). Some of our observations may be the result of detection bias due to increased medical surveillance among patients with severe autoimmune disorders, and the use of a hospitalized cohort might have resulted in underascertainment of cancer cases and milder autoimmune conditions, and did not capture those diagnosed in outpatient settings. Potential confounding variables may not have been reliably assessed using inpatient hospital records. Furthermore our results are generalizable only to black and white males. Finally, due to the large number of autoimmune conditions and alimentary tract cancer sites evaluated in our analysis, some of the observed associations could have occurred by chance alone.

In conclusion, we found that a prior history of certain autoimmune diseases with known alimentary tract involvement was associated with an increased risk of developing alimentary tract cancers, potentially supporting the importance of localized inflammation in alimentary tract carcinogenesis. If our findings are confirmed, future investigations designed to dissect

underlying mechanisms between specific autoimmune conditions and alimentary tract cancers will provide clues to etiology and pathogenesis, allow identification of novel molecular targets, and may ultimately lead to early detection or prevention.

Acknowledgments

We thank the Medical Administration Service of the U.S. Veterans Health Services and Research Administration for providing the data on which this study is based. We also thank the IMS programmers Eric Boyd and David Campbell for their dedicated and diligent work.

Sources of support that requires acknowledgement including grant numbers: This research was supported by the Intramural Research Program of the National Cancer Institute, NIH, DHHS.

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Table 1

Selected characteristics of 4,501,578 U.S. male Veterans included in this analysis

	No solid cancer	Any cancer of the alimentary tract
Total number of persons included in the study	4,155,320	96,277
African American	764,291	20,797
Whites	3,391,029	75,480
Mean age at study entry	50.74	57.67
Total years of follow-up	49,963,253	719,216
Mean years of follow-up	12.02	7.47
Maximum years of follow-up	26.25	26.22
Median number of hospital visits	2	4

Table 2

Relative risk of developing cancer of the alimentary tract in relation to a personal history of autoimmune disease

	Buccal			Esophagus			Stomach			Small intestine		
Autoimmune disease (ICDA/ICD9-CM)	**N**	**RR**	**(95% CI)***	**N**	**RR**	**(95% CI)***	**N**	**RR**	**(95% CI)***	**N**	**RR**	**(95% CI)***
With alimentary tract involvement												
Ankylosing spondylitis (7124/7200)	47	**0.64**	**(0.48, 0.86)**	26	1.11	(0.75, 1.64)	21	1.08	(0.69, 1.67)	-		
Celiac disease (269.0/579.0)	19	1.09	(0.69, 1.70)	11	**1.86**	**(1.03, 3.36)**	-			-		
Crohn's disease (5630/555)	30	0.77	(0.53, 1.11)	12	0.89	(0.49, 1.61)	8	0.76	(0.38, 1.52)	11	**8.24**	**(4.53, 14.99)**
Discoid lupus erythematosus (6954/6954)	63	**1.77**	**(1.38, 2.27)**	18	1.34	(0.84, 2.12)	9	0.95	(0.48, 1.90)	-		
Immune thrombocytopenic purpura (2871/2873)	107	**1.38**	**(1.14, 1.69)**	36	**1.57**	**(1.13, 2.17)**	9	0.58	(0.28, 1.22)	-		
Localized scleroderma (701.0/701.0)	7	1.23	(0.59, 2.59)	5	**2.40**	**(1.00, 5.76)**	-			-		
Pernicious anemia (2810/2810)	85	**1.45**	**(1.17, 1.80)**	30	1.38	(0.96, 1.98)	68	**3.17**	**(2.47, 4.07)**	5	**2.67**	**(1.10, 6.45)**
Polyarteritis nodosa (4460/4460)	8	1.95	(0.98, 3.90)	-			-			-		
Primary biliary cirrhosis (5718/5716)	124	**1.38**	**(1.15, 1.65)**	35	1.29	(0.93, 1.81)	23	**1.66**	**(1.10, 2.51)**	-		
Reactive arthritis (Reiter's disease) (136/993)	24	1.33	(0.89, 1.99)	12	**2.05**	**(1.16, 3.61)**	-			-		
Sarcoidosis (135/135)	30	1.00	(0.69, 1.44)	12	0.76	(0.42, 1.37)	5	0.57	(0.24, 1.37)	-		
Sjögren's syndrome (7349/7102)	20	1.41	(0.90, 2.22)	-			-			-		
Systemic lupus erythematosus (7341/7100)	17	1.09	(0.68, 1.75)	8	1.22	(0.58, 2.55)	8	1.53	(0.73, 3.21)	-		
Systemic sclerosis (7340/7101)	23	1.41	(0.90, 2.22)	15	**2.86**	**(1.72, 4.74)**	5	1.04	(0.39, 2.77)	-		
Ulcerative colitis (5631/556)	44	0.75	(0.55, 1.02)	16	0.83	(0.50, 1.38)	19	1.11	(0.70, 1.76)	5	**2.53**	**(1.05, 6.11)**
Without alimentary tract involvement												
Addison disease (2551/2554)	25	1.34	(0.88, 2.03)	11	1.31	(0.68, 2.51)	11	1.62	(0.84, 3.11)	-		
Amyotrophic lateral sclerosis (3480/3352)	25	0.86	(0.57, 1.30)	8	0.77	(0.38, 1.54)	9	0.91	(0.45, 1.81)	-		
Autoimmune hemolytic anemia (2839/2830)	22	1.09	(0.71, 1.70)	8	1.12	(0.56, 2.24)	6	1.10	(0.46, 2.65)	-		
Chronic rheumatic heart disease (393–8/393–8)	308	**0.84**	**(0.75, 0.94)**	124	0.87	(0.72, 1.05)	125	1.00	(0.83, 1.21)	8	0.61	(0.29, 1.28)
Graves' disease (2420/2420)	21	**0.55**	**(0.35, 0.87)**	9	0.64	(0.33, 1.23)	12	1.07	(0.61, 1.88)	-		
Hashimoto thyroiditis (2451/2452)	6	0.90	(0.40, 2.00)	-			-			-		
Multiple sclerosis (340/340)	39	**0.43**	**(0.31, 0.59)**	14	**0.45**	**(0.26, 0.78)**	18	0.71	(0.45, 1.13)	-		
Myasthenia gravis (7330/3580)	6	0.45	(0.19, 1.07)	-			-			-		
Polymyalgia rheumatica (- /725)	-			-			-			-		
Psoriasis (6960–1/6960–1)	359	1.11	(0.99, 1.23)	106	1.16	(0.96, 1.41)	79	1.11	(0.88, 1.41)	10	1.41	(0.75, 2.63)

Autoimmune disease (ICDA/ICD9-CM)	Buccal			Esophagus			Stomach			Small intestine		
	N	RR	(95% CI)*	N	RR	(95% CI)*	N	RR	(95% CI)*	N	RR	(95% CI)*
Rheumatic fever (390–1/390–1)	25	1.03	(0.69, 1.54)	10	1.24	(0.67, 2.31)	-			-		
Rheumatoid arthritis (712/714)	348	**0.84**	**(0.75, 0.94)**	140	0.98	(0.83, 1.16)	120	0.98	(0.82, 1.18)	10	0.82	(0.44, 1.53)

Autoimmune disease (ICDA/ICD9-CM)	Colon			Rectum			Liver			Pancreas		
	N	RR	(95% CI)*	N	RR	(95% CI)*	N	RR	(95% CI)*	N	RR	(95% CI)*
With alimentary tract involvement												
Ankylosing spondylitis (7124/7200)	60	1.00	(0.77, 1.29)	34	1.01	(0.72, 1.42)	11	0.78	(0.42, 1.45)	22	1.04	(0.68, 1.59)
Celiac disease (269.0/579.0)	11	0.85	(0.47, 1.54)	9	1.29	(0.67, 2.48)	-			13	**2.27**	**(1.22, 4.23)**
Crohn's disease (5630/555)	52	1.30	(0.97, 1.76)	25	1.05	(0.69, 1.62)	10	1.09	(0.57, 2.10)	17	1.26	(0.76, 2.09)
Discoid lupus erythematosus (6954/6954)	26	1.02	(0.68, 1.52)	11	0.83	(0.46, 1.51)	9	1.33	(0.69, 2.57)	10	1.02	(0.53, 1.97)
Immune thrombocytopenic purpura (2871/2873)	51	**1.39**	**(1.05, 1.83)**	27	1.26	(0.85, 1.86)	81	**6.76**	**(5.41, 8.46)**	8	0.63	(0.31, 1.25)
Localized scleroderma (701.0/701.0)	-			-			-			-		
Pernicious anemia (2810/2810)	59	0.80	(0.61, 1.04)	38	1.00	(0.71, 1.40)	18	1.29	(0.79, 2.10)	25	1.08	(0.70, 1.66)
Polyarteritis nodosa (4460/4460)	-			-			-			-		
Primary biliary cirrhosis (5718/5716)	46	1.14	(0.85, 1.53)	21	1.00	(0.65, 1.54)	80	**6.01**	**(4.76, 7.57)**	33	**2.06**	**(1.44, 2.96)**
Reactive arthritis (Reiter's disease) (136/993)	9	0.77	(0.38, 1.53)	-			5	1.50	(0.62, 3.60)	-		
Sarcoidosis (135/135)	29	1.40	(0.96, 2.04)	22	**1.99**	**(1.31, 3.03)**	5	0.76	(0.32, 1.83)	12	1.20	(0.64, 2.23)
Sjögren's syndrome (7349/7102)	12	0.99	(0.55, 1.79)	-			-			-		
Systemic lupus erythematosus (7341/7100)	19	1.23	(0.76, 1.98)	6	0.74	(0.33, 1.65)	-			7	1.40	(0.67, 2.93)
Systemic sclerosis (7340/7101)	12	1.01	(0.56, 1.83)	5	0.81	(0.34, 1.96)	-			-		
Ulcerative colitis (5631/556)	112	**2.06**	**(1.70, 2.48)**	66	**2.07**	**(1.62, 2.64)**	30	**2.43**	**(1.69, 3.50)**	22	1.10	(0.71, 1.71)
Without alimentary tract involvement												
Addison disease (2551/2554)	13	0.60	(0.32, 1.11)	10	1.09	(0.59, 2.03)	-			9	1.06	(0.47, 2.35)
Amyotrophic lateral sclerosis (3480/3352)	26	0.83	(0.55, 1.25)	10	0.64	(0.34, 1.18)	-			6	0.65	(0.29, 1.44)
Autoimmune hemolytic anemia (2839/2830)	16	1.21	(0.74, 1.97)	11	1.42	(0.76, 2.64)	8	2.08	(0.99, 4.36)	9	1.28	(0.58, 2.85)
Chronic rheumatic heart disease (393–8/393–8)	424	**1.15**	**(1.04, 1.27)**	178	0.91	(0.78, 1.06)	76	0.87	(0.68, 1.11)	132	1.03	(0.86, 1.24)
Graves' disease (2420/2420)	25	0.76	(0.51, 1.13)	17	0.90	(0.55, 1.46)	-			-		
Hashimoto thyroiditis (2451/2452)	6	0.98	(0.44, 2.18)	-			-			-		
Multiple sclerosis (340/340)	72	0.92	(0.73, 1.16)	37	0.73	(0.52, 1.03)	7	**0.42**	**(0.20, 0.89)**	18	**0.62**	**(0.39, 0.99)**
Myasthenia gravis (7330/3580)	14	1.00	(0.59, 1.69)	6	0.79	(0.35, 1.75)	-			-		

Autoimmune disease (ICDA/ICD9-CM)	Colon			Rectum			Liver			Pancreas		
	N	RR	(95% CI)*	N	RR	(95% CI)*	N	RR	(95% CI)*	N	RR	(95% CI)*
Polymyalgia rheumatica (- /725)	10	0.94	(0.47, 1.89)	7	1.27	(0.57, 2.82)	-			-		
Psoriasis (6960–1/6960–1)	210	0.99	(0.86, 1.13)	137	1.13	(0.95, 1.34)	74	1.23	(0.97, 1.55)	76	1.06	(0.84, 1.33)
Rheumatic fever (390–1/390–1)	25	1.28	(0.86, 1.91)	10	0.94	(0.50, 1.74)	5	1.05	(0.44, 2.53)	9	1.32	(0.69, 2.54)
Rheumatoid arthritis (712/714)	350	0.93	(0.84, 1.04)	184	0.89	(0.76, 1.03)	81	0.96	(0.76, 1.21)	120	0.91	(0.75, 1.09)

Bold font indicates statistically significant (P<0.05) associations.

- indicates risk estimates are not reported because fewer than five cases were observed.

* RR(95%CI) adjusted for attained age and calendar year, race, number of hospital visits, and latency. RR(95%CI) for buccal, esophageal, and liver cancers were also adjusted for alcohol.

Abbreviations: N, number; RR, relative risk; CI, confidence interval.

Table 3

Potential confounding co-morbid conditions identified from discharge diagnoses at VA hospitals as defined by the 8th and 9th revisions of the International Classification of Diseases (ICDA, ICD9-CM)

Comorbid condition	ICDA	ICD9-CM
Smoking-related diagnoses		
Emphysema	492	492
Bronchitis	491	491
COPD excluding asthma	490,491,492	490,491,492,494,495,496
COPD including asthma	490,491,492,493	490,491,492,493,494,495,496
Hypertension	400,401,402,403,404	401,402,403,404,405
Alcoholism	291,303,5710,9800	291,303,5353,5710, 5711,5712,5713,9800
Diabetes mellitus	250	250
Obesity	277	2780
HIV	-	042
Hepatitis viral	070	070
Hepatitis (acute,chronic)	070,5719	070,5714
GERD	5301,5302,5303,5533	5301,5302,5303,5533
Infectious mononucleosis	075	075

Abbreviations: Chronic obstructive pulmonary disease (COPD), Gastroesophageal reflux disease (GERD), human immunodeficiency virus (HIV).

- indicates that no code was available