HHS Public Access

Author manuscript

Am J Gastroenterol. Author manuscript; available in PMC 2023 March 01.

Published in final edited form as:

Am J Gastroenterol. 2022 March 01; 117(3): 486–490. doi:10.14309/ajg.0000000000001622.

Associations between Autoimmune Conditions and Gastric Cancer Risk among Elderly Adults in the United States

Minkyo Song, MD, PhD[1] **[Guarantor]**, **M. Constanza Camargo, PhD**[1], **Andriy Derkach, PhD**[1], **Charles S. Rabkin, MD**[1], **Eric A. Engels, MD, MPH**[1]

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland, USA.

Abstract

Introduction: Pernicious anemia (PA) is a risk factor for gastric cancer. Other autoimmune conditions may also contribute.

Methods: In a case-control study, we evaluated 47 autoimmune conditions among 39,125 gastric cancers and 200,000 cancer-free controls.

Results: Six conditions were associated with increased gastric cancer risk (range of adjusted odds ratios [ORs]: 1.28-1.93, $p<0.05$): PA, membranous nephropathy, primary biliary cirrhosis, pure red cell aplasia, primary sclerosing cholangitis, and Graves' disease. PA was associated with 8 other autoimmune conditions (adjusted ORs: 1.57-4.54, $p<0.05$).

Conclusions: Autoimmune conditions associated with gastric cancer or PA may reflect effects of autoimmune gastritis or other carcinogenic pathways.

Keywords

Autoimmunity; Gastric Cancer; Epidemiology; Elderly

INTRODUCTION

Pernicious anemia (PA) has been associated with gastric cancer (1, 2). With waning prevalence of *Helicobacter pylori* infection, the relative significance of this alternative etiologic pathway involving autoimmunity may grow (3). Notably, recent increases in gastric cancer among certain groups implicate autoimmunity as a possible cause (4). Several autoimmune diseases besides PA have been associated with gastric cancer risk (5).

Correspondence to: Name: Minkyo Song, Address: Infections and Immunoepidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Drive, 6E204, Bethesda, MD 20892-9776, Phone: 240-276-7985, Fax: 240-276-7806, minkyo.song@nih.gov.

Specific author contributions: ICMJE criteria for authorship read and met: all authors; Agree with the manuscript's results and conclusions: all authors; Designed the study: MS, CSR, EAE; Collected the data: MS, EAE; Analyzed the data: MS; Wrote the first draft of the paper: MS; Contributed to the writing of the paper: MS, EAE; Interpretation of the data, approved the final version of the manuscript: all authors; Supervised the project: MS, EAE

Potential competing interests: None.

Writing Assistance: None.

The global prevalence of autoimmune conditions is rising (6). Therefore, it is important to assess their impact on cancer incidence. We comprehensively evaluated associations between autoimmune conditions and gastric cancer among elderly adults in the United States. We further explored associations of autoimmune conditions with PA, which we hypothesize may mediate associations between some conditions and gastric cancer.

MATERIALS AND METHODS

In a population-based case-control study using the Surveillance Epidemiology and End Results (SEER)-Medicare linked database (7), we identified gastric cancer cases with a first cancer diagnosis during 1992-2015. A total of 200,000 cancer-free controls were selected from the 5% random sample of Medicare beneficiaries included in SEER-Medicare, frequency-matched to cases by calendar year of selection, age category (66-69, 70-74, 75-79, 80-84, 85-99 years), sex and race (non-Hispanic White, non-Hispanic Black, other/unknown). We identified autoimmune conditions using Medicare claims, requiring documentation of autoimmune conditions in one hospital claim or two provider or outpatient claims at least 30 days apart. We evaluated 47 different autoimmune conditions but the results for 11 conditions with ≤10 affected cases are not presented (Supplementary Table 1).

Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using unconditional logistic regression (7), adjusting for matching variables, average number of physician visits per year, zip code-based median income, smoking, and alcohol abuse (Supplementary Table 2). We used a Bonferroni correction to determine statistical significance (p-value cutoff 0.05/47=0.001). Significant associations were assessed for heterogeneity by sex. We conducted exploratory analyses for anatomical subsites, for which $p<0.05$ was considered significant (nominal significance). Furthermore, we assessed the association of conditions with PA among controls. See the Supplementary Methods for additional details.

RESULTS

The study included 39,125 gastric cancer cases and 200,000 cancer-free controls (Supplementary Table 3). Having any autoimmune conditions was positively associated with gastric cancer (OR 1.16, 95%CI 1.13-1.20). Six autoimmune conditions were nominally associated with increased risk of gastric cancer: PA, membranous nephropathy, primary biliary cirrhosis, pure red cell aplasia (PRCA), primary sclerosing cholangitis, and Graves' disease (OR range 1.28-1.93, Figure 1). Two were associated with reduced gastric cancer risk: Takayasu arteritis and celiac disease (ORs 0.58-0.73). After Bonferroni correction, only PA and PRCA remained significant. The association between PRCA and gastric cancer was similar after additional adjustments for PA (Supplementary Table 4).

A sex-stratified analysis revealed stronger PA and gastric cancer association in women (OR 2.17, 95%CI 1.99-2.37) than men (1.67, 1.51-1.85, $P_{heterogeneity}<0.0001$), but not for PRCA ($P_{heterogeneity}=0.47$). As shown in Table 1, the magnitude of association was stronger for noncardia than cardia gastric cancers with any autoimmune condition (OR 1.16 vs 1.08, respectively; $P_{heterogeneity}=0.0004$) and PA (2.03 vs 1.27; $P_{heterogeneity} < 0.0001$) but not PRCA (1.50 vs 1.00; $P_{heterogeneity}=0.07$).

Among controls, PA was most strongly associated with aplastic anemia, followed by Crohn's disease, PRCA, polymyositis/dermatomyositis, celiac disease, Addison's disease, rheumatoid arthritis, and ulcerative colitis (OR range 1.75-4.54, Figure 2).

DISCUSSION

To our knowledge, this is the largest, most comprehensive study evaluating associations between autoimmune conditions and gastric cancer. Having any autoimmune condition was associated with a small increased risk of gastric cancer. We confirmed the known strong association with PA and found a novel independent association with PRCA.

PA is caused by autoimmune gastritis, which may increase gastric cancer risk through chronic increase in gastric pH and gastrin secretion (8). The association with PA was strongest for noncardia gastric cancer, which matches the anatomy of autoimmune gastritis (9). We are the first to report a difference in the association between PA and gastric cancer by sex. This stronger association among women may reflect a higher prevalence of other cofactors in men, such as cigarette smoking or *H. pylori* infection.

Notably, we found PRCA to be associated with both gastric cancer and PA. There are limited case studies of co-occurrence of PRCA and PA (10), and PRCA with gastric cancer (11). The restricted association of PRCA with noncardia gastric cancer supports that autoimmune gastritis may mediate this association.

Conditions that showed associations with gastric cancer but not with PA may act through pathways that do not involve autoimmune gastritis. These autoimmune conditions may exacerbate gastritis caused by *H. pylori*, or *H. pylori* may cause these autoimmune conditions (12). Autoimmune conditions associated only with PA probably do not have direct mechanistic links to gastric carcinogenesis, and positive results in published literature may reflect their associations with PA (5).

The strengths of our study include its population-based design and large sample size. Our study is larger than an earlier SEER-Medicare study (2), and we included 7-10 times more gastric cancers with autoimmune diseases than studies in Sweden (13) and among US veterans (14). The large size enabled us to explore associations between rare autoimmune diseases and gastric cancer, and with its anatomical subsites.

However, we could not assess some factors related to gastric cancer risks, such as *H. pylori* infection, family history of gastric cancer, salty food consumption, and autoimmune disease treatments. The results may not be generalizable to younger people or non-White individuals (who were under-represented). Medical claims data are inherently limited in diagnostic accuracy. Clinical conditions could not be ascertained before age 65, so some autoimmune conditions may have been underdiagnosed. Finally, the rarity of autoimmune conditions and gastric cancer limited our ability to detect associations with small effect sizes.

Rising trends in autoimmunity may account for the increasing incidence of gastric cancer among certain populations. Additional research may provide evidence for developing

strategies in assessing gastric cancer risk, which may facilitate early detection and improve cancer outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

This study used the linked SEER-Medicare database. The authors acknowledge the efforts of the National Cancer Institute; the Office of Research, Development and Information, CMS; Information Management Services (IMS), Inc.; and the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. The authors would also like to acknowledge Winnie Ricker at IMS for providing analytical support. This study was supported by the Intramural Research Program of the National Cancer Institute.

ABBREVIATIONS

CI	confidence interval
OR	odds ratios
PA	pernicious anemia
PRCA	pure red cell aplasia
SEER	Surveillance Epidemiology and End Results

REFERENCES

1. Vannella L, Lahner E, Osborn J, et al. Systematic review: gastric cancer incidence in pernicious anaemia. Aliment Pharmacol Ther 2013;37:375–82. [PubMed: 23216458]
2. Murphy G, Dawsey SM, Engels EA, et al. Cancer Risk After Pernicious Anemia in the US Elderly Population. Clin Gastroenterol Hepatol 2015;13:2282–9 e1-4. [PubMed: 26079040]
3. Song M, Rabkin CS, Camargo MC. Gastric Cancer: an Evolving Disease. Curr Treat Options Gastroenterol 2018;16:561–569. [PubMed: 30361856]
4. Anderson WF, Rabkin CS, Turner N, et al. The Changing Face of Noncardia Gastric Cancer Incidence Among US Non-Hispanic Whites. J Natl Cancer Inst 2018.
5. Song M, Latorre G, Ivanovic-Zuvic D, et al. Autoimmune Diseases and Gastric Cancer Risk: A Systematic Review and Meta-Analysis. Cancer Res Treat 2019.
6. Lerner A, Jeremias P, Matthias T. The World Incidence and Prevalence of Autoimmune Diseases is Increasing. International Journal of Celiac Disease 2015;3:151–155.
7. Engels EA, Pfeiffer RM, Ricker W, et al. Use of surveillance, epidemiology, and end results-medicare data to conduct case-control studies of cancer among the US elderly. Am J Epidemiol 2011;174:860–70. [PubMed: 21821540]
8. Hakanson R, Sundler F. Trophic effects of gastrin. Scand J Gastroenterol Suppl 1991;180:130–6. [PubMed: 1710370]
9. Neumann WL, Coss E, Rugge M, et al. Autoimmune atrophic gastritis--pathogenesis, pathology and management. Nat Rev Gastroenterol Hepatol 2013;10:529–41. [PubMed: 23774773]
10. Dan K, Ito T, Nomura T. Pure red cell aplasia following pernicious anemia. Am J Hematol 1990;33:148–50. [PubMed: 2105636]
11. Gajwani B, Zinner EN. Pure red-cell aplasia. Associated with adenocarcinoma of stomach. N Y State J Med 1976;76:2177–9. [PubMed: 1069208]

12. Hasni S, Ippolito A, Illei GG. Helicobacter pylori and autoimmune diseases. Oral Dis 2011;17:621–7. [PubMed: 21902767]
13. Hemminki K, Liu X, Ji J, et al. Autoimmune disease and subsequent digestive tract cancer by histology. Ann Oncol 2012;23:927–33. [PubMed: 21810731]
14. Landgren AM, Landgren O, Gridley G, et al. Autoimmune disease and subsequent risk of developing alimentary tract cancers among 4.5 million US male veterans. Cancer 2011;117:1163–71. [PubMed: 21381009]

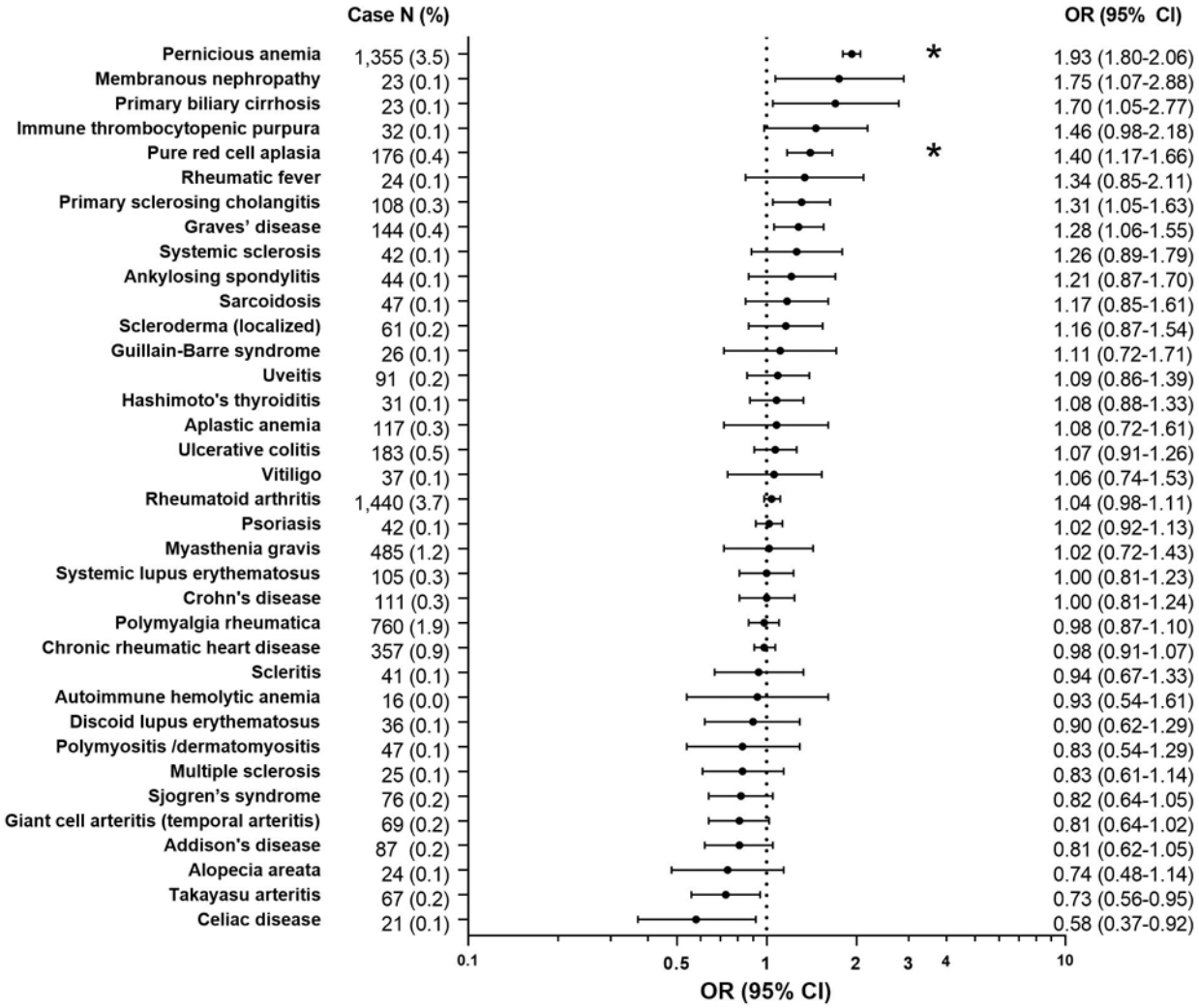

Figure 1. Association of autoimmune conditions with gastric cancer

Odds ratios are adjusted for age, sex, race/ethnicity, calendar year of cancer diagnosis/ control selection, average number of physician visits per year, zip code median income, smoking, and alcohol abuse. Asterisk (*) indicates association is significant at the Bonferroni p-value threshold.

Abbreviations: CI, confidence interval; OR, odds ratio

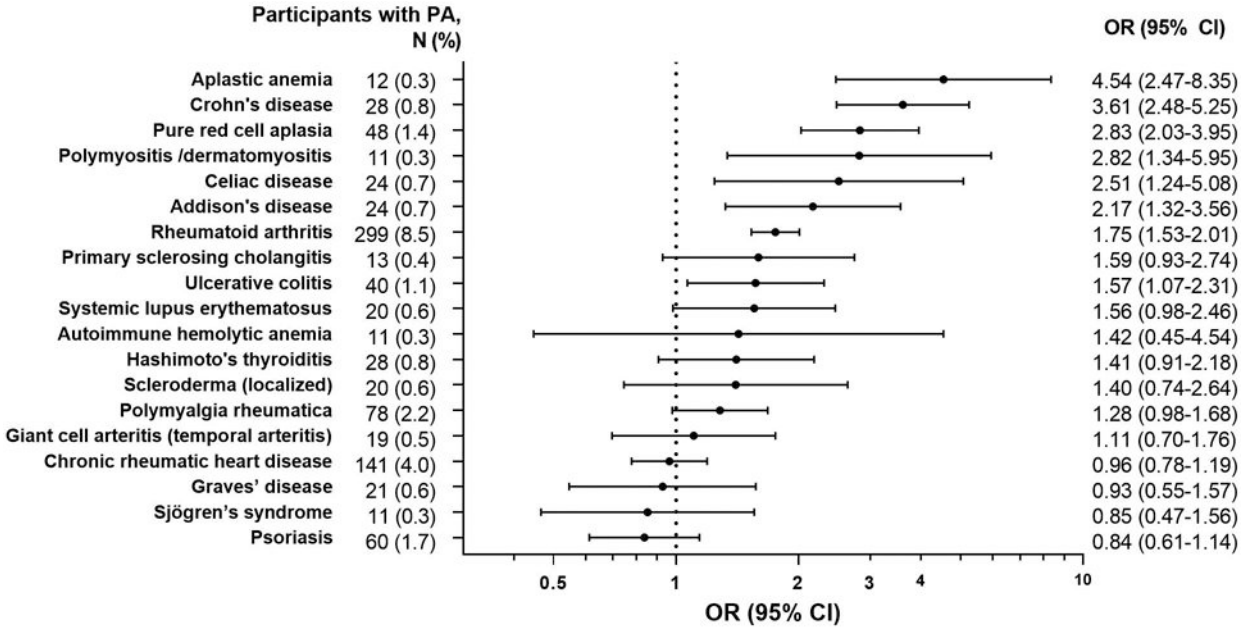

Figure 2. Associations of autoimmune conditions with pernicious anemia among control individuals

Odds ratios are adjusted for age, sex, race/ethnicity, calendar year of cancer diagnosis/ control selection, average number of physician visits per year, zip code median income, smoking, and alcohol abuse.

Abbreviations: CI, confidence interval; OR, odds ratio; PA, pernicious anemia

Table 1.

Associations between autoimmune conditions and gastric cancer risk, according to cancer subsite

Conditions	Control		Cardia (n=10,169)			Noncardia (n=19,453)			Others/Unspecified (n=9,503)		
	N	%	N	%	OR (95%CI)	N	%	OR (95%CI)	N	%	OR (95%CI)
Addison's disease	406	0.2	14	0.1	0.62 (0.36-1.06)	34	0.2	0.80 (0.56-1.15)	21	0.2	1.06 (0.68-1.64)
Alopecia areata	165	0.1				17	0.1	0.94 (0.57-1.56)			
Ankylosing spondylitis	175	0.1	11	0.1	0.96 (0.52-1.78)	20	0.1	1.18 (0.74-1.88)	13	0.1	1.61 (0.91-2.86)
Aplastic anemia	138	0.1				17	0.1	1.09 (0.65-1.84)			
Celiac disease	179	0.1				11	0.1	0.67 (0.36-1.23)			
Chronic rheumatic heart disease	3,580	1.8	229	2.3	1.11 (0.96-1.27)	341	1.8	0.89 (0.79-1.00)	190	2.0	1.06 (0.91-1.23)
Crohn's disease	507	0.3	25	0.2	0.78 (0.52-1.18)	57	0.3	1.16 (0.88-1.53)	23	0.2	0.95 (0.62-1.45)
Discoid lupus erythematosus	197	0.1				15	0.1	0.71 (0.42-1.21)	12	0.1	1.21 (0.67-2.19)
Giant cell arteritis (temporal arteritis)	522	0.3	25	0.2	1.00 (0.66-1.51)	46	0.2	0.84 (0.61-1.14)	16	0.2	0.60 (0.36-0.99)
Graves' disease	553	0.3	26	0.3	0.98 (0.66-1.46)	86	0.4	**1.48 (1.17-1.86)**	32	0.3	1.17 (0.82-1.68)
Guillain-Barré syndrome	112	0.1				13	0.1	1.12 (0.63-1.99)			
Hashimoto's thyroiditis	538	0.3	30	0.3	1.07 (0.73-1.55)	61	0.3	1.15 (0.88-1.51)	26	0.3	1.00 (0.67-1.50)
Immune thrombocytopenic purpura	107	0.1				16	0.1	1.60 (0.94-2.73)			
Membranous nephropathy	65	0.0				11	0.1	1.67 (0.86-3.23)			
Multiple sclerosis	282	0.1	16	0.2	0.97 (0.58-1.62)	19	0.1	0.72 (0.45-1.16)	12	0.1	0.91 (0.51-1.63)
Myasthenia gravis	203	0.1	13	0.1	1.00 (0.56-1.77)	18	0.1	0.94 (0.57-1.53)	11	0.1	1.19 (0.64-2.19)
Pernicious anemia	3,532	1.8	225	2.2	**1.27 (1.10-1.46)**	717	3.7	**2.03 (1.86-2.21)**	413	4.3	2.46 (2.21-2.74)
Polymyalgia rheumatica	1,802	0.9	91	0.9	0.98 (0.79-1.22)	176	0.9	0.97 (0.83-1.14)	90	0.9	1.00 (0.81-1.25)
Primary sclerosing cholangitis	399	0.2	17	0.2	0.85 (0.52-1.39)	71	0.4	**1.64 (1.26-2.13)**	20	0.2	1.03 (0.66-1.63)
Psoriasis	2,352	1.2	164	1.6	1.15 (0.98-1.36)	211	1.1	0.93 (0.81-1.08)	110	1.2	1.01 (0.83-1.23)
Pure red cell aplasia	597	0.3	30	0.3	1.00 (0.69-1.46)	99	0.5	**1.50 (1.20-1.87)**	47	0.5	**1.56 (1.15-2.11)**
Rheumatic fever	87	0.0				12	0.1	1.32 (0.72-2.43)			
Rheumatoid arthritis	6,731	3.4	293	2.9	0.93 (0.82-1.05)	774	4.0	1.06 (0.98-1.14)	373	3.9	**1.12 (1.01-1.25)**
Sarcoidosis	198	0.1				29	0.1	1.38 (0.93-2.05)	15	0.2	1.56 (0.92-2.67)
Scleritis	209	0.1	11	0.1	1.13 (0.60-2.12)	18	0.1	0.76 (0.47-1.25)	12	0.1	1.19 (0.66-2.15)
Scleroderma (localized)	260	0.1	18	0.2	1.54 (0.95-2.48)	30	0.2	1.13 (0.77-1.66)	13	0.1	0.98 (0.56-1.72)
Sjögren's syndrome	456	0.2	19	0.2	0.92 (0.58-1.46)	39	0.2	0.80 (0.58-1.12)	18	0.2	0.79 (0.49-1.27)

Am J Gastroenterol. Author manuscript; available in PMC 2023 March 01.

Conditions	Control		Cardia (n=10,169)			Noncardia (n=19,453)			Others/Unspecified (n=9,503)		
	N	%	N	%	OR (95%CI)	N	%	OR (95%CI)	N	%	OR (95%CI)
Systemic lupus erythematosus	542	0.3	21	0.2	0.82 (0.53-1.28)	55	0.3	0.95 (0.71-1.26)	35	0.4	1.29 (0.91-1.83)
Systemic sclerosis	159	0.1	12	0.1	1.71 (0.94-3.10)	18	0.1	1.03 (0.62-1.69)	12	0.1	1.46 (0.80-2.65)
Takayasu arteritis	438	0.2	16	0.2	0.66 (0.40-1.10)	38	0.2	0.83 (0.59-1.16)	13	0.1	0.60 (0.34-1.04)
Ulcerative colitis	841	0.4	60	0.6	1.19 (0.91-1.56)	83	0.4	1.02 (0.81-1.29)	40	0.4	1.02 (0.74-1.40)
Uveitis	411	0.2	14	0.1	0.82 (0.48-1.40)	50	0.3	1.10 (0.81-1.49)	27	0.3	1.32 (0.88-1.96)
Vitiligo	174	0.1				21	0.1	1.13 (0.71-1.80)			
Any autoimmune condition	24,459	12.2	1,346	13.2	**1.08 (1.02-1.15)**	2,862	14.7	**1.16 (1.11-1.21)**	1,455	15.3	**1.28 (1.20-1.36)**

Entries for the number of affected cases are not presented when the number is ≤10, in accordance with the SEER-Medicare data use agreement. Odds ratios are adjusted for age, sex, race/ethnicity, calendar year of cancer diagnosis/control selection, average number of physician visits per year, zip code median income, smoking, and alcohol abuse.

Bolded results indicate nominal significance ($p<0.05$).

Abbreviations: CI, confidence interval; OR, odds ratio