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Review Article

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Autoimmune Diseases and Gastric Cancer Risk: A Systematic Review and Meta-Analysis

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Purpose

Autoimmunity is an alternative etiology of gastric inflammation, the initiating event in the gastric carcinogenic cascade. This mechanism may be an increasingly important cause of gastric cancer with the waning prevalence of its primary etiologic factor, chronic *Helicobacter pylori* infection.

Materials and Methods

PubMed and EMBASE were searched up to September 2018. Autoimmunity and 96 specific manifestations were considered for associations with gastric cancer risk. Random effects analysis was used to calculate pooled relative risk estimates (RR) and 95% confidence intervals (CI).

Results

We found a total of 52 observational studies representing 30 different autoimmune diseases. Overall, the presence of an autoimmune condition was associated with a gastric cancer pooled RR of 1.37 (95% CI, 1.24 to 1.52). Among the 24 autoimmune conditions with two or more independent reports, nine were significantly associated with increased gastric cancer risk: dermatomyositis (RR, 3.69; 95% CI, 1.74 to 7.79), pernicious anemia (RR, 2.84; 95% CI, 2.30 to 3.50), Addison disease (RR, 2.11; 95% CI, 1.26 to 3.53), dermatitis herpetiformis (RR, 1.74; 95% CI, 1.02 to 2.97; n=3), IgG4-related disease (RR, 1.69; 95% CI, 1.00 to 2.87), primary biliary cirrhosis (RR, 1.64; 95% CI, 1.13 to 2.37), diabetes mellitus type 1 (RR, 1.41; 95% CI, 1.20 to 1.67), systemic lupus erythematosus (RR, 1.37; 95% CI, 1.01 to 1.84), and Graves disease (RR, 1.27; 95% CI, 1.06 to 1.52).

Conclusion

Our analysis documents the wide range of autoimmune diseases associated with gastric cancer. These associations may reflect unreported links between these conditions and autoimmune gastritis. Further studies are warranted to investigate potential causal mechanisms.

Key words
Stomach neoplasms, Autoimmune diseases, Epidemiology, Risk

Introduction

While still the third leading cause of cancer death and the fifth most common cancer worldwide, gastric cancer incidence and mortality have markedly declined over the past few decades [1]. The downward trend has paralleled the decreasing prevalence of *Helicobacter pylori* infection [2], a major risk factor for this malignancy. However, cancer registration data indicate unexpected increases among recent generations in many parts of the world [3-5], implying etiologic factors other than *H. pylori* may be responsible [6].

Inflammation is a recognized antecedent of many types of cancer. Autoimmune conditions are important causes of inflammation and appear to have increased in prevalence over recent decades [7], particularly in industrialized popu-

lations. An association with gastric cancer has been firmly established for the immune-mediated destruction of the gastric parietal cells, autoimmune gastritis, and its most common clinical manifestation, pernicious anemia [8]. Other autoimmune conditions have been variably linked with gastric cancer risk, perhaps as a consequence of their frequent co-occurrence with autoimmune gastritis or, alternatively, through some systemic effect(s) that remains to be elucidated. To better understand the role of autoimmunity in gastric carcinogenesis, we undertook a systematic review and meta-analysis of observational studies addressing associations of autoimmune diseases and gastric cancer risk.

Materials and Methods

1. Search strategy and inclusion criteria

PubMed (U.S. National Library of Medicine, Bethesda, MD) and EMBASE (Elsevier B.V., Amsterdam, The Netherlands) search engines were used to identify published articles on gastric cancer risk in patients with autoimmune diseases by combining terms for (1) "stomach cancer" with synonyms, (2) "autoimmune disease" with synonyms or 96 specific autoimmune diseases with synonyms, and (3) "risk" with synonyms. The search strategy syntax was as follows: (1) ['stomach cancer'/exp OR 'cancer, stomach' OR 'gastric cancer' OR 'stomach cancer' OR 'gastric neoplasm'], AND (2) ['autoimmune disease'/exp OR 'auto immune disease' OR 'auto immunologic disease' OR 'auto-immune disorder' OR 'auto-immune disorders' OR 'autoaggression, immune' OR 'autoaggressive disease' OR 'autoantibody disease' OR 'autoimmune disease' OR 'autoimmune diseases' OR 'autoimmune disorder' OR 'autoimmune disorders' OR 'autoimmune disturbance' OR 'autoimmune pathology' OR 'autoimmune disease' OR 'autoimmunologic disease' OR (96 autoimmune diseases with their synonyms)], AND (3) ['risk'/exp OR 'risk' OR 'risk hypothesis' OR 'cancer risk'/exp OR 'cancer risk' OR 'risk factor'/exp OR 'relative risk' OR 'risk factor' OR 'risk factors']. The list of specific autoimmune diseases was generated by combining the 92 terms listed as autoimmune diseases in the National Library of Medicine controlled vocabulary thesaurus for indexing articles, Medical Subject Headings (MeSH), and the EMBASE equivalent, Emtree, with pernicious anemia, autoimmune gastritis, celiac disease and primary biliary cirrhosis. The full list of autoimmune conditions and their syntax can be found in S1 and S2 Tables.

Literature searches were conducted for database entries through September 30, 2018, without restriction on language or article type. Reference lists of retrieved articles were also checked for additional papers that were not identified by our database search strategy. Two investigators (G.L. and D.I.Z.) independently reviewed the articles for relevance and availability of basic information, with any disagreement resolved by a third reviewer (M.C.C.). After the initial scanning of titles and abstracts, full text of selected articles was obtained for data extraction. Articles retained for the final analysis were those with either case-counts or risk estimates reported as standardized incidence ratio (SIR), standardized mortality ratio, incident rate ratio, adjusted rate ratio, hazard ratio, relative risk (RR), or odds ratio. The following data were extracted as available: first author, year of publication, study design, study period, sex, country of origin, regional group, type of autoimmune disease, sample size, tumor subsite, risk estimates and their corresponding 95% confidence intervals (CI), and adjusted confounders (S3 Table). The methodological quality of each selected publication was evaluated using the Newcastle-Ottawa Scale for cohort and case-control studies, summarized in S4 and S5 Tables, respectively [9]. We considered a study scoring ≥ 7 to be high quality. Sensitivity analysis restricting to high quality studies was conducted where applicable. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting [10].

2. Statistical analyses

Summary estimates preferentially included the associations for total populations in a study rather than a subgroup (e.g., males and females combined rather than single sex, and gastric cancer overall rather than separate anatomical subsites). If there was no overall value presented, associations for subgroups (e.g., males and females) were included as separate studies. Standardized ratios or adjusted rates were used when available, but the association measures were derived based on the study design when only observed and expected case counts were provided. Summary risk estimates were calculated if there were two or more studies published for a given autoimmune condition. For selected diseases with common features, we also estimated associations for the combined group. We also evaluated associations with "alimentary tract involving diseases," following previous reports [11,12].

Random-effects regression models were used to meta-analyze the summary risk estimates as RR with corresponding 95% CIs [13]. Heterogeneity among studies was assessed with Cochran's Q test and Higgin's I^2 statistics [14]. Publication bias was evaluated by Begg's funnel plots and Egger's tests [15]. Funnel plot asymmetry was examined with the trim and fill method of Duval and Tweedie [16]. To explore sources of heterogeneity, meta-regressions were con-

Table 1. Random effects summary relative risk (RR) and 95% confidence interval (CI) of gastric cancer for persons with autoimmune disease

Autoimmune disease	Studies included for analysis	Gastric cancer cases	Summary RR	95% CI	Cochran Q statistic ($p_{heterogeneity}$)	Higgin's I^2 statistics	Egger test p-value	Studies imputed by trim and fill
Individual diagnoses								
Addison disease	2	20	2.11	1.26-3.53	1.26 (0.26)	20.5	-	0
Amyotrophic lateral sclerosis	2	13	0.93	0.53-1.62	0.01 (0.93)	0	-	1
Ankylosing spondylitis	2	34	1.01	0.72-1.42	0.21 (0.65)	0	-	0
Celiac disease	7	80	1.36	0.87-2.13	18.53 (< 0.001)	73	0.59	0
Chronic rheumatic heart disease	2	184	1.19	0.86-2.13	8.28 (< 0.001)	87.9	-	0
Crohn disease	3	60	0.87	0.68-1.12	0.24 (0.89)	0	0.91	0
Dermatitis herpetiformis	3	13	1.74	1.02-2.97	1.07 (0.59)	0	0.07	2
Dermatomyositis	4	11[a)]	3.69	1.74-7.79	5.10 (0.16)	41.2	0.66	2[b)]
Diabetes mellitus, type 1	9	256[a)]	1.41	1.20-1.67	12.45 (0.13)	35.7	0.89	0[b)]
Graves disease	3	120	1.27	1.06-1.52	0.81 (0.67)	0	0.09	0
IgG4-related disease	2	6	1.69	1.00-2.87	0.58 (0.45)	0	-	1
Immune thrombocytopenic purpura	2	15	1.32	0.26-6.70	9.03 (< 0.001)	88.9	-	1
Multiple sclerosis	2	30	0.64	0.45-0.92	0.47 (0.50)	0	-	0
Pernicious anemia	14	2,688	2.84	2.30-3.50	73.98 (< 0.001)	82.4	0.32	0[b)]
Polymyositis	2	2	0.82	0.12-5.55	2.30 (0.13)	56.6	-	0
Polymyositis/Dermatomyositis	2	7	1.15	0.16-8.25	4.42 (0.04)	77.4	-	0
Primary biliary cirrhosis	4	28	1.64	1.13-2.37	0.32 (0.96)	0	0.66	1
Psoriasis	2	128	1.18	0.98-1.14	0.58 (0.45)	0	-	1
Rheumatoid arthritis	10	388	0.93	0.82-1.07	15.78 (0.07)	43.0	0.38	1
Sarcoidosis	2	36	1.00	0.41-2.44	3.75 (0.05)	73.4	-	0
Sjögren syndrome	4	27[a)]	1.33	0.99-1.79	3.15 (0.37)	4.6	0.05	1
Systemic lupus erythematosus	6	35[a)]	1.37	1.01-1.84	4.85 (0.30)	17.6	0.12	0[b)]
Systemic sclerosis	5	12[a)]	0.93	0.58-1.48	0.56 (0.97)	0	0.74	0
Ulcerative colitis	3	45	0.94	0.70-1.26	0.95 (0.62)	0	0.27	0

(Continued to the next page)

Table 1. Continued

Autoimmune disease	Studies included for analysis	Gastric cancer cases	Summary RR	95% CI	Cochran Q statistic ($p_{heterogeneity}$)	Higgin's I^2 statistics	Egger test p-value	Studies imputed by trim and fill
Grouped diagnoses[c]								
Autoimmune thyroid disease		163	1.31	1.12-1.54	3.84 (0.43)	0	0.77	0
Inflammatory bowel disease		105[a]	0.89	0.74-1.07	1.19 (0.93)	0	0.34	0
Polymyositis/Dermatomyositis		20[a]	2.09	1.04-4.20	17.59 (0.01)	60.2	0.10	0
Polymyalgia rheumatica/Giant cell arteritis		202	1.33	1.16-1.52	0.78 (0.38)	0	-	1
Vasculitides		38	1.03	0.75-1.41	1.89 (0.60)	0	0.84	0
Alimentary tract involving autoimmune diseases other than pernicious anemia		391[a]	1.18	1.04-1.33	60.16 (0.01)	36.8	0.86	0[b]
Non-alimentary tract involving autoimmune diseases		1,736[a]	1.21	1.10-1.34	182.77 (< 0.001)	67.7	0.43	10[b]
Endocrine organ autoimmune diseases		521[a]	1.42	1.25-1.61	21.39 (0.13)	29.9	0.65	0[b]
Non-endocrine organ autoimmune diseases other than pernicious anemia		1,607[a]	1.15	1.06-1.26	202.72 (< 0.001)	59.6	0.51	9[b]
Any autoimmune disease other than pernicious anemia		627[a]	1.20	1.11-1.30	243.13 (< 0.001)	59.7	0.60	9[b]
Any autoimmune disease		3,315[a]	1.37	1.24-1.52	685.72 (< 0.001)	83.7	0.18	0[b]

[a]One or more studies did not provide number of cases, [b]Retained significance after trim and fill imputation, [c]Grouped diagnoses definitions (numbers of studies included): autoimmune thyroid disease: autoimmune thyroid disease (1), Graves disease (3), Hashimoto/hypothyroidism (1); inflammatory bowel disease: Crohn disease (3), inflammatory bowel disease (1), ulcerative colitis (3); polymyositis/dermatomyositis: dermatomyositis (2), polymyositis (1), polymyositis/dermatomyositis (1); polymyalgia rheumatica/giant cell arteritis: polymyalgia rheumatica (1), polymyalgia rheumatica/giant cell arteritis (1); vasculitides: antineutrophil cytoplasmic antibody associated vasculitis (1), polyarteritis nodosa (1), Takayasu arteritis (1), Wegener granulomatosis (1); alimentary tract involving autoimmune diseases: ankylosing spondylitis (2), celiac disease (7), Crohn disease (3), discoid lupus erythematosus (1), immune thrombocytopenic purpura (2), inflammatory bowel disease (1), localized scleroderma (1), pernicious anemia (16), primary biliary cirrhosis (4), sarcoidosis (2), Sjögren syndrome (4), systemic lupus erythematosus (7), systemic sclerosis (5), ulcerative colitis (3); endocrine organ autoimmune diseases: Addison disease (2), autoimmune thyroid disease (5), diabetes mellitus, type 1 (11); any autoimmune disease: includes all diagnoses listed in Tables 1 or 2.

ducted according to study design (case-control, retrospective cohort, or prospective cohort), year of publication (< 2,000 vs. ≥ 2,000), geographic area (Asia, Europe, USA, or multiple), sex (male, female or combined) and tumor subsite (cardia vs. noncardia). Statistical analyses were conducted using STATA SE 15 software (StataCorp., College Station, TX). All statistical tests were two-sided and p-values of < 0.05 were considered statistically significant.

Results

A total of 1,134 articles were identified after removing the duplicates through the database search (S6 Fig.). Of these, 964 articles were excluded as irrelevant on the basis of title or abstract. The remaining 170 articles were reviewed for full-text as well as their references, and finally 52 studies with relevant and extractable information were included for meta-analysis. The full list of included articles and the corresponding data items are presented in S3 Table. There were 12 prospective cohort studies, 36 retrospective cohort studies and four case-control studies. Most of the studies were conducted in Western populations (30 European studies, six in the United States and one multi-country effort). There were 15 studies from Asia. Forty-one of the 52 papers were judged high quality. A total of 45 different autoimmune conditions were reported in these studies, amongst which 30 conditions had two or more studies for pooling. However, six of these 30 included studies with zero cases and insufficient information (such as expected cancers) for deriving risk estimates.

Table 1 lists associations of 24 autoimmune conditions with gastric cancer risk. The strongest associations were observed for dermatomyositis (RR, 3.69; 95% CI, 1.74 to 7.79), pernicious anemia (RR, 2.84; 95% CI, 2.30 to 3.50), and Addison disease (RR, 2.11; 95% CI, 1.26 to 3.53). Other autoimmune conditions that were statistically significantly associated with gastric cancer risk were dermatitis herpetiformis, IgG4-related disease, primary biliary cirrhosis, diabetes mellitus type 1 (T1DM), and systematic lupus erythematosus (SLE). Among disease groups, statistically significant increases were observed for polymyositis/dermatomyositis combined with RR 2.09 (95% CI, 1.04 to 4.20), polymyalgia rheumatica/giant cell arteritis with RR 1.33 (95% CI, 1.16 to 1.52) and autoimmune thyroid disease with RR 1.31 (95% CI, 1.12 to 1.54). Multiple sclerosis was the only condition associated with statistically significant decreased risk, RR 0.64 (95% CI, 0.45 to 0.92). Excluding pernicious anemia, pooled risk estimates for alimentary tract-involving and non-alimentary autoimmune conditions were 1.18 (95% CI, 1.04 to 1.33) and 1.21 (95% CI, 1.10 to 1.34), respectively. Autoimmune diseases that involve endocrine glands, which include Addison disease, autoimmune thyroiditis and T1DM had pooled RR 1.42 (95% CI, 1.25 to 1.61), whereas autoimmune non-

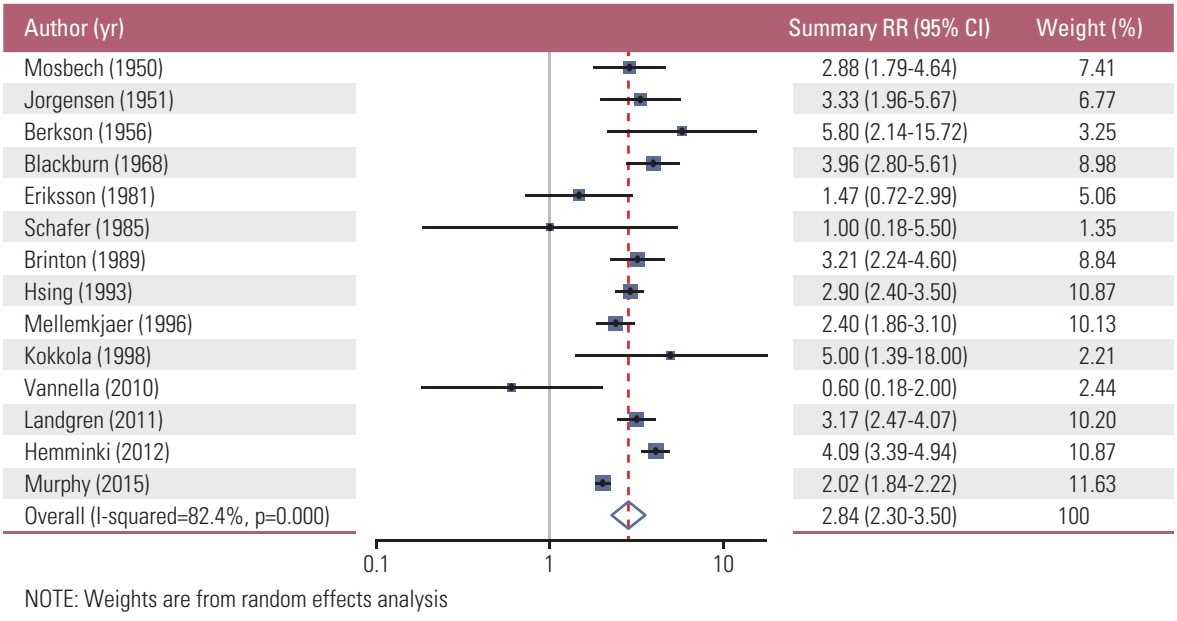

Fig. 1. Random effects summary relative risk (RR) and 95% confidence interval (CI) for gastric cancer among individuals with pernicious anemia [11,12,17-28].

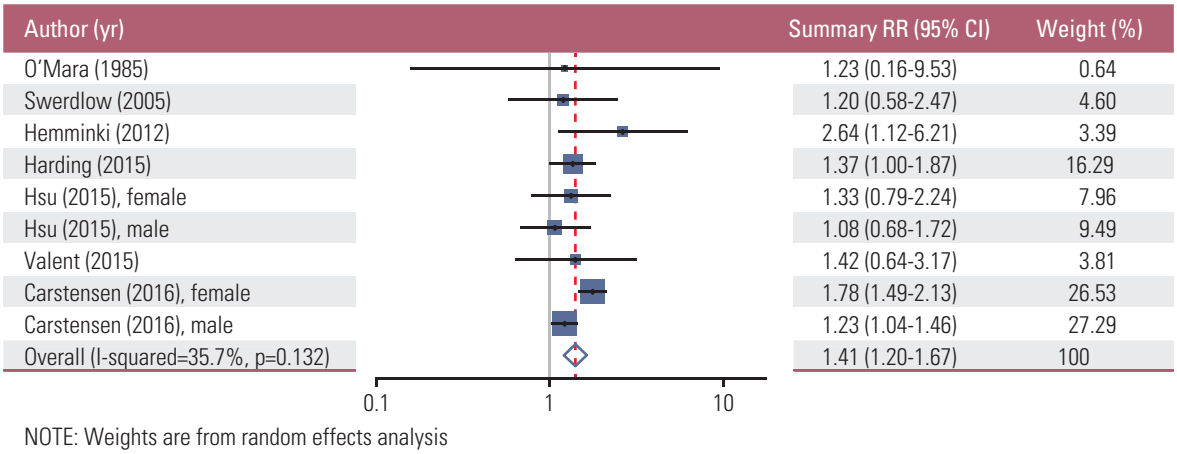

Fig. 2. Random effects summary relative risk (RR) and 95% confidence interval (CI) for gastric cancer among individuals with diabetes mellitus type 1 [11,29-34].

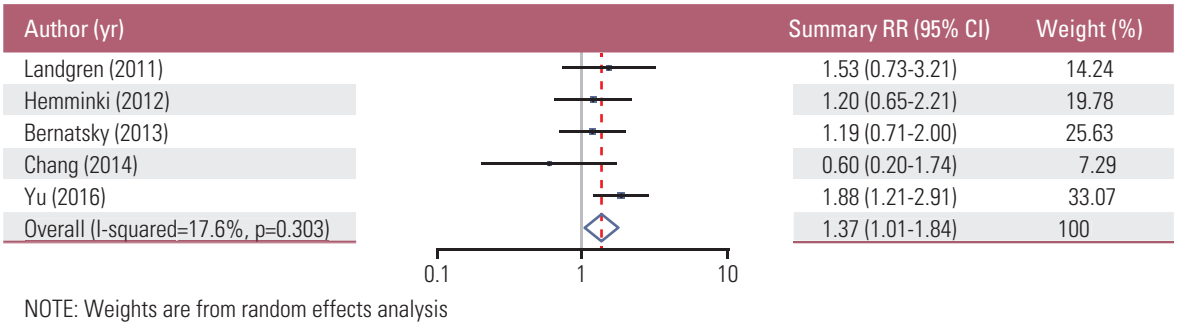

Fig. 3. Random effects summary relative risk (RR) and 95% confidence interval (CI) for gastric cancer among individuals with systemic lupus erythematosus [11,12,35-37].

endocrine diseases other than pernicious anemia had pooled RR 1.15 (95% CI, 1.06 to 1.26; $p_{heterogeneity}$=0.008). Considering all reports combined, having any autoimmune condition was associated with statistically significant pooled RR 1.37 (95% CI, 1.24 to 1.52).

There were no reports of gastric cancer with pernicious anemia in the studies from Asia. Considering all other autoimmune diseases combined, the summary RR for gastric cancer was 1.08 (95% CI, 0.90 to 1.29) in studies from Asia compared to 1.24 (95% CI, 1.14 to 1.34) in studies from non-Asian countries ($p_{heterogeneity}$=0.005).

Funnel plots were symmetric for all conditions. Imputation of hypothetical missing results by the trim and fill method did not alter the estimated associations by more than 20% with the exception of immune thrombocytopenic purpura for which change in RR was 56%.

Pernicious anemia, T1DM and SLE each had more than 5 studies for analysis and are displayed separately as forest plots in Figs. 1-3.

There was marked heterogeneity among the 14 studies of the association of pernicious anemia with gastric cancer overall, indicated by I^2=82.4% and p-value of < 0.001 (Fig. 1) [11,12,17-28]. Sensitivity analyses restricted to cohort studies (n=13; RR, 2.94; 95% CI, 2.37 to 3.65) and high quality studies (n=12; RR, 2.70; 95% CI, 2.15 to 3.40) were similar to our overall pooled RR.

A low heterogeneity among studies was observed in the meta-analysis of T1DM (n=9) association with I^2=35.7% and p=0.13 (Fig. 2) [11,29-34]. For the four studies with sex information, the association was significantly greater in females (RR, 1.77; 95% CI, 1.51 to 2.07) compared to males (RR, 1.19; 95% CI, 1.03 to 1.39) ($p_{heterogeneity}$ < 0.001).

Gastric cancer RR with SLE showed low heterogeneity among studies (n=6) with I^2=17.6% and p=0.303 (Fig. 3)

Table 2. Reported associations of gastric cancer with autoimmune diseases from single studies

Disease	Exposed persons	Gastric cancer persons	Reported association
Autoimmune pancreatitis type 1	109	3	1.35 (0.03-2.66)
ANCA associated vasculitis: GPA and MPA[a)]	203	1	2.37 (0.06-13.2)
Alopecia areata	12,199	39	0.46 (0.33-0.65)
Autoimmune hemolytic anemia	NR	6	1.10 (0.46-2.65)
Autoimmune thyroid disease[a)]	23	17	3.16 (1.14-8.71)
Behçet disease	2,860	11	1.66 (0.83-2.99)
	1,620	0	NR
Discoid lupus erythematosus	NR	9	0.95 (0.48-1.90)
Hashimoto/hypothyroidism[a)]	10,682	26	1.34 (0.87-1.96)
Inflammatory bowel disease[a)]	2,853	NR	0.53 (0.13-2.11)
Kawasaki disease	3,463	0	NR
Localized scleroderma	3,128	11	1.56 (0.70-2.55)
	NR	0	NR
Membranous nephropathy	161	1	2.74 (0.07-15.3)
Myasthenia gravis	17,974	117	1.38 (1.14-1.65)
	NR	0	NR
Polyarteritis nodosa	12,046	35	1.02 (0.71-1.42)
	NR	0	NR
Polymyalgia rheumatica[a)]	14,745	63	1.45 (1.11-1.85)
	NR	0	NR
Polymyalgia rheumatica/Giant cell arteritis[a)]	35,918	139	1.27 (1.07-1.50)
Reactive arthritis	NR	0	NR
Rheumatic fever	3,458	16	1.50 (0.86-2.44)
	NR	0	NR
Takayasu arteritis	180	1	1.4 (0.0-7.3)
Vasculitis excluding Kawasaki disease	644	0	NR
Wegener granulomatosis[a)]	345	1	0.45 (0.0-2.59)

ANCA, antineutrophil cytoplasmic antibody; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiits; NR, not reported. [a)]Also included in Table 1 grouped diagnoses.

[11,12,35-38].

The 15 conditions with only one study report and the additional six with insufficient information for pooling are summarized in Table 2. Apart from those diseases mentioned in Table 1, statistically significant associations were reported for myasthenia gravis (RR, 1.38; 95% CI, 1.14 to 1.65) [11] and alopecia areata (RR, 0.46; 95% CI, 0.33 to 0.65) [39].

Discussion

This is the first comprehensive review of autoimmune conditions in gastric cancer risk. Our meta-analysis identified significant associations for autoimmunity overall and for several specific conditions. We extended the known association of pernicious anemia with greater statistical power. By pooling all available evidence to date, we found novel associations for some autoimmune diseases which showed inconsistent or null results in individual studies.

There was a modest increase of gastric cancer risk across all autoimmune conditions combined. Autoimmunity could be linked with gastric carcinogenesis through different potential pathways. Many of the conditions associated with gastric cancer in this study, such as autoimmune thyroiditis, T1DM, vitiligo, and Addison disease, frequently cooccur with pernicious anemia, which has a direct mechanistic interpretation through its pathological correlate, autoimmune gastritis. Indeed, the overall association of autoimmune conditions with gastric cancer was significantly weaker in studies from Asia than from other parts of the world, consistent with the relatively lower incidence of pernicious anemia in Asian populations [40]. Alternatively,

autoimmunity might exacerbate *H. pylori*–driven gastritis in the absence of autoimmune gastritis *per se*. For either of these scenarios, the etiologic contributions of other components of the gastric microbiome remains to be determined.

In the study of 4.5 million U.S. male veterans [12], autoimmune diseases with alimentary tract involvement were associated with an increased risk of alimentary tract cancers, including gastric cancer, whereas conditions without alimentary tract involvement generally were not significantly associated. Using the same definition of alimentary tract involvement and excluding pernicious anemia, we found no difference in gastric cancer risk between alimentary tract-involving versus all other conditions. On the other hand, when we grouped the non-pernicious anemia autoimmune conditions based on endocrine gland involvement, gastric cancer risk was significantly higher for autoimmune endocrine diseases than for the remainder. Given that pernicious anemia results from destruction of secretory parietal cells, these observations reinforce the intriguing concept that the autoimmune component of gastric carcinogenesis is more closely linked to glandular targets than to the alimentary tract *per se*.

Epidemiologic evidence for an autoimmune contribution to gastric carcinogenesis is not limited to studies of patients with personal history of autoimmune conditions. In a study linking the Swedish Multigeneration Register and the Swedish Cancer Register, family history of autoimmune disease in siblings was associated with noncardia gastric cancer with SIR 1.36 (95% CI, 1.22 to 1.52) [41]. On the other hand, autoimmune disease in spouses was not associated. Taken together, these observations favor an underlying basis that is related to either genes or childhood environment (shared by siblings), rather than adult exposures (shared by spouses).

Although based on only a limited number of studies, multiple sclerosis and alopecia areata showed significant inverse association with gastric cancer. Both of these diseases share similar characteristics of increased T helper type 1 immune activation and altered cytokine levels which were postulated to have inhibitory effects on carcinogenesis [12,39].

Our study has some limitations and thus the results should be interpreted with caution. First, like many other studies investigating patient populations, the effect of treatments for autoimmune conditions could not be fully addressed. Immunosuppressive medications or immunomodulatory drugs, such as steroids, cytotoxic agents and nonsteroidal anti-inflammatory drugs, may themselves affect gastric carcinogenesis. There may also be decreased medical surveillance in severely debilitating diseases which might explain the inverse association for multiple sclerosis. Second, despite our attempt to include all available literature, only a relatively small number of studies met inclusion criteria, and many autoimmune diseases had insufficient data for a meta-analysis. However, autoimmune diseases with small numbers of studies and comparisons that lack statistical significance should not be interpreted as evidence against association. Third, most of the studies were based in Western populations and prevalence of many autoimmune diseases varies across race/ethnicity and geographical location, limiting generalizability of the pooled risk estimates. Fourth, autoimmune diseases are underdiagnosed conditions, and some degree of misclassification of exposure is likely. Such nondifferential misclassification would tend to attenuate true associations between autoimmune disease and gastric cancer. Fifth, as in any meta-analysis, possible publication bias is a concern although we did not find evidence for missing information with trim and fill correction. Sixth, clinical assessment of autoimmune diseases may vary across the studies. Lastly, gastric cancer risk factors such as *H. pylori* infection or smoking were not taken into account in many of these studies.

Despite the above limitations, our study has many strengths. Our systematic review is the first attempt to comprehensively summarize current evidence associating autoimmunity with gastric cancer risk. By pooling small studies, we were able to increase power for novel findings. Most of the studies were prospective investigations of incident gastric cancer, minimizing the possibility of reverse causality. Lastly, most of the included studies were classified as good quality.

The rarity of autoimmune diseases with their characteristic predominance in females, developed countries and Western populations, combined with the opposite profile for gastric cancer burden (males, under-developed countries, Asians), may have hampered recognition of the links between these entities. Future studies are warranted to investigate these associations in different races and ethnic groups, by anatomical subsite or tumor histology, and with consideration of treatment effects. Moreover, our findings may have important clinical and public health implications. The apparent increases in autoimmune disease and the newly recognized relation to gastric cancer risk have important implications for predicting future cancer incidence and planning strategies for control and prevention.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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