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Review

Multiple Associations Between a Broad Spectrum of Autoimmune Diseases, Chronic Inflammatory Diseases and Cancer

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Abstract. *Background: Many recent studies suggest the immune system plays a significant role in the pathogenesis of autoimmune diseases, chronic inflammatory diseases, and cancer. Materials and Methods: Literature published between 2001 and 2011 was reviewed for risk of cancer development in patients with autoimmune and chronic inflammatory diseases. Mode of risk assessment employed did not limit inclusion of studies. Autoimmune conditions developing after diagnosis of a pre-existing cancer were also considered. Results: We report a pervasive, largely positive association between 23 autoimmune and inflammatory diseases and subsequent cancer development. We discuss associations for celiac disease, inflammatory bowel disease rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis in detail. We also address the less frequently reported development of some autoimmune conditions within the course of some malignancies, such as vitiligo developing in the course of melanoma. Conclusion: Evidence demonstrates that chronic inflammation and autoimmunity are associated with the development of malignancy. Additionally, patients with a primary malignancy may develop autoimmune like disease. These relationships imply a need for surveillance of patients on immunomodulatory therapies for potential secondary disease processes.*

As the development and use of immunomodulatory therapies for cancer and autoimmune diseases increase, understanding the breadth of functions of the human immune system is increasingly necessary. Here, we discuss an important area of research: identifying the relationships between autoimmunity and chronic inflammatory disease and cancer.

With a goal of translating findings to improve human health, the field of tumor immunology characterizes the interface of the immune system with cancer. Evidence suggests that parts of the immune system may generate anticancer responses, while other parts may promote cancer (Figure 1). In a state of perpetual activation, immune mediators, such as cytokines, chemokines and free radicals, may cause tissue damage leading to chronic inflammation, and subsequently increase the risk of carcinogenesis (1-4). Additionally, ongoing stimulation and subsequent rapid proliferation of the immune cells in this setting may contribute to malignant lymphoproliferation (5, 6). Other factors affecting immune activity, such as genetic mutations, environmental exposure, and immunomodulatory treatments, may also bolster a carcinogenic environment (1-6).

Alternatively, numerous observations suggest that the immune system inhibits cancer progression. For example, when patients are on long-term immunosuppressive medications, such as cyclosporine for preventing graft-*versus*-host disease after organ transplantation, odds of cancer development are increased (7, 8). Patients who are immunocompromised by HIV infection are more susceptible to development of some malignancies, including AIDS defining cancer such as Kaposi's sarcoma and central nervous system (CNS) lymphomas, as well as lung cancer and Hodgkin's lymphoma (9). In addition, similar to introducing a novel virus into a population, cancer in transplanted organs may develop rapidly in recipients, although malignancies were unapparent or in remission in the donor (10).

On a cellular level, T-cells in the tumor environment contribute to antitumor immune activity by interacting with antigen-presenting molecules displaying tumor-associated antigens (TAA), antigenic proteins expressed by a tumor that are unique, mutated, or even normal self-proteins with up-regulated expression (11, 12). In response to interactions

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Key Words: Autoimmunity, cancer immunity, inflammation, paraneoplastic disease, celiac disease, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, review.

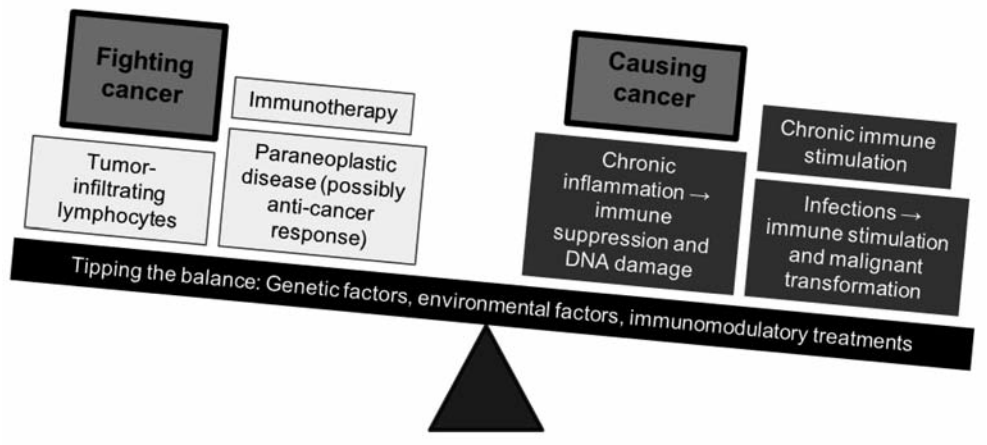

Figure 1. *Immune responses can both promote and counteract carcinogenesis. An immune response is essential for protection against the development of cancer, yet activation of the immune system may lead to loss of self-tolerance and induction of autoimmunity. Various factors contributing to the careful balance of the immune response are indicated above (1-6, 11).*

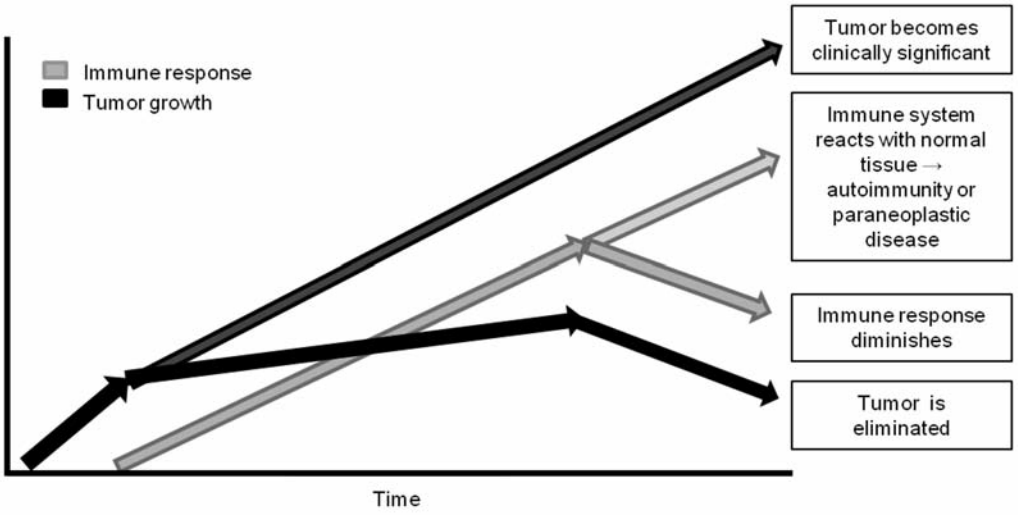

Figure 2. *Immune response to cancer over time. This diagram represents the growth of a hypothetical tumor (black), the ensuing immune response (grey), and potential clinical outcomes over time (11, 12).*

with TAA, tumor-infiltrating lymphocytes (TIL) may produce effector molecules, including granzymes, perforins, cytokines, and interferon (IFN)-γ that are directly cytotoxic to tumor cells. In a number of studies, detection of TIL in most tumors directly correlates with improved prognosis and patient survival (11, 12), and ideally, this interaction completely eliminates the neoplasm (Figure 2). If the immune system does not kill the malignant growth, it may become clinically significant (11, 12). Tumor escape may also occur if the effector immune response is induced to tolerate the neoplasm. Regulatory T-cells (Tregs), specifically $FOXP3^+$ $CD25^+$ $CD4^+$ Tregs, suppress immune activity and migrate into tumors and draining lymph nodes, dampening the antitumor immune response. Additional data show that depletion of Tregs from tumors results in a decrease in immunological tolerance and improved antitumor immunity (13). Alternatively, successful antitumor responses may cross-react with normal self tissues, losing self-tolerance. Consequently, if the magnitude of the immune response continues to enlarge, inflammatory or autoimmune disease may develop (14-23).

Thus, the immune system may either aid in the prevention of or augment the promotion of carcinogenesis. Clinical observations and cellular research support the idea that

Table I. *Overview of statistical calculations included as primary risk assessments.*

Risk calculation and abbreviation		Notes
Relative risk	RR	Drawn from cohort studies Significant values represent a variable with true etiological risk for a given condition (126)
Standardized incidence ratio	SIR	Estimates RR from a population- or registry-based group of subjects Used as an estimate for RR when the prevalence of the investigated variable is low (126)
Odds ratio	OR	Valid effect measures typically based on data from case-control studies Overestimate RR when odds of having a true association are high (127)
Hazard ratio	HR	Represents the odds of an event occurring within a given amount of time or the effect of a variable on the time to an undesired outcome (128)
Incidence rate ratio	IRR	Ratios of incidences of a condition between two groups Significant risk of confounding factors (129)
Adjusted rate ratio	ARR	Similar to IRR but attempts to account for potential confounders
Standardized morbidity ratio	SMR	Compares incidence of a morbidity within a population of interest to incidence of the same morbidity within a standardized control population (130)

malignancies may stimulate an antitumor immune response; however, inflammatory processes may contribute to cancer progression, and multiple associations of autoimmune and chronic inflammatory diseases with cancer have accordingly been demonstrated. In this review, by evaluating a large breadth of recent literature, we attempt to document these associations to present a broad perspective of the burgeoning associations of autoimmune diseases, chronic inflammatory diseases, and cancer.

Materials and Methods

Autoimmune and chronic inflammatory conditions were identified through the American Autoimmune-Related Diseases Association, Inc. A PubMed search was performed using broad search terms for all fields of "cancer," "neoplasms," and common names for the autoimmune or chronic inflammatory disease investigated. "Neoplasms" was also included in the search as a MeSH term. Results were limited to articles published in English from 2001 to 2011. Over 1,400 articles were drawn from the primary search based on abstracts addressing a general risk association between autoimmunity and cancer, specific autoimmune diseases and cancer risk, and cancer associated with paraneoplastic autoimmune phenomena. These articles were reviewed in detail for association calculations describing a relationship between the specific inflammatory condition and cancer. Literature reviewed included primary research of case control, cohort and retrospective analyses, review articles, editorials, and case reports. Results reported here focus on diseases which were recurrently noted in the literature, and thus, 23 inflammatory and autoimmune conditions were included based on the frequency of reported association with cancer; infrequently associated cancers were also removed for conciseness. Despite evidence predicting a possible link between immunomodulatory medication regimens and cancer (5, 6), we did not explore this area here due to the wide variety and often only recent availability of these treatments. No time cut-off for patient observation periods in the studies was employed. Autoimmune conditions which occurred in the setting of previously diagnosed cancer were also considered, and although statistical calculations for their associations were largely unavailable, recurring observations are reported here.

Results were drawn from articles which contain primary association calculations between neoplastic diseases and autoimmune-related diseases. Significant associations from these articles were recorded (*i.e.* the calculated 95% confidence interval does not include the value 1, risk unchanged). Multiple types of association calculations were considered and are summarized in Table I.

Results

A review of the literature revealed significant associations between 23 different autoimmune and chronic inflammatory autoimmune-related diseases and cancer (Tables II and III). Of these observed relationships, celiac disease had some of the strongest and most extensive associations with both focal organ and lymphoproliferative malignancies. Celiac disease is a complex condition in which immune intolerance for naturally ingested wheat protein, gluten, and antibodies towards tissue transglutaminases lead to the development of significant enteropathy and associated symptoms (Figure 3). Patients who are positive for human lymphocyte antigen classes DQ2 or DQ8 are particularly affected by increased binding of antigen-presenting cells to deamidated gluten, allowing for induction of a $CD4^+$ helper T-cell-mediated inflammatory response (24). This response includes IFN-γ release and $CD8^+$ T-cell activation, which leads to tissue damage and gut cytotoxicity, creating a pro-malignancy chronic inflammatory state. One group evaluating this connection was that of Askling *et al*., who used Swedish National Registers to follow a cohort of approximately 11,000 patients with celiac disease to evaluate cancer incidence over an average of 9.8 years (25). This group calculated a standardized incidence ratio (SIR) of 10 for small bowel malignancy, 4.2 for esophageal cancer, and 6.3 for non-Hodgkin's lymphoma (NHL) among other significant

Table II. *Reported associations between autoimmune diseases, chronic inflammatory diseases, and focal malignancies.*

Autoimmune/chronic inflammatory disease	All cancer	Focal malignancy										
		Lung	Kidney	Bladder	Brain	Endocrine	Thyroid	Breast	Ovary	Cervix	Endometrium	Prostate
Addison disease	-	-	-	-	-	-	-	-	-	-	-	-
Ankylosing spondylitis	-	-	-	-	-	-	-	-	-	-	-	-
Autoimmune hemolytic anemia	-	-	-	-	-	-	-	-	-	-	-	-
Celiac disease	1.3 (25)	-	-	-	-	3.0 (25)	{22.52} (PTC)(131)	0.2 (132) 0.3 (25)	-	-	-	-
Crohn's disease	1.27* (26) 1.54 (33) 2.24 (78)	1.50 (33)	2.29 (33)	-	-	1.92 (33)	-	-	-	2.63* (26)	-	1.19 (33)
Dermatitis herpetiformis	-	-	-	-	-	-	-	-	-	-	-	-
Graves disease	1.13 (112)	-	-	-	-	2.20 (112)	12.08 (112)	1.14 (112)	-	-	-	-
Hashimoto thyroiditis	-	-	-	-	-	-	2.96 (PTC)(133)	-	-	-	-	-
Idiopathic thrombocytopenic purpura	-	-	-	-	-	-	-	-	-	-	-	-
Multiple sclerosis	[0.91] (45)	0.63 (79) [0.69] (45)	-	-	1.3 (46) [1.44] (45)	-	-	1.21 (79)	[0.58] (45)	-	-	0.53 (79) [0.80] (45)
Myasthenia gravis	-	-	-	-	-	-	-	-	-	-	-	-
Pernicious anemia	-	-	-	-	-	-	-	-	-	-	-	-
Primary biliary cirrhosis	-	-	-	-	-	-	-	-	-	-	-	-
Psoriasis	*1.13* (80) 1.37 (71) 1.33 (72)	1.78 (72) 2.13 (71)	1.50 (72) 1.56 (71)	1.43 (71) 1.51 (72) [3.18] (82)	1.42 (72)	-	-	1.27 (71)	-	-	-	-

Autoimmune/chronic inflammatory disease	All GI cancer	Focal GI malignancy										
		Buccal/Oral	Upper aero/GI tract	Esophageal	Stomach	Small bowel	Colon	Colorectal	Rectum	Anus	Liver	Pancreas
Addison disease	-	-	-	5.54 (98)	2.74 (98)	-	-	-	-	-	-	-
Ankylosing spondylitis	-	**0.64** (67)	-	-	-	-	-	-	-	-	-	-
Autoimmune hemolytic anemia	-	-	-	-	-	-	-	-	-	-	-	-
Celiac disease	[5.95]** (99)	-	-	**1.86** (67) 4.2 (25) {12} (27)	3 (132)	10 (25) 25 (132) {34} (27)	1.9 (25)	-	-	-	2.7 (25)	**2.27** (67)
Crohn's disease	-	-	-	-	-	**8.24**(67) 11.05 (98) 12.07 (100) 13.82 (33) {66.67} (91)	1.64* (26) 2.76 (98) 2.93 (33)	1.45 (101) 5.80 (78)	1.55 (33) 1.83 (98)	3.1 (74)	2.57 (33)	1.89 (33)
Dermatitis herpetiformis	-	-	-	-	-	-	-	-	-	-	-	-
Graves disease	-	**0.55** (67)	1.36 (98) 1.56 (112)	-	1.31 (98)	-	0.78 (112)	-	-	-	-	-
Hashimoto thyroiditis	-	-	1.70 (98)	-	-	-	-	-	-	-	-	-
Idiopathic thrombocytopenic purpura	-	**1.38** (67)	-	**1.57** (67)	3.04 (98)	-	**1.39** (67) 2.61 (98)	-	-	-	**6.76** (67)	-
Multiple sclerosis	0.8 (79) [0.83] (45)	**0.43** (67)	-	**0.45** (67)	[0.62] (45)	-	-	-	-	-	**0.42** (67)	**0.62** (67) [0.67] (45)
Myasthenia gravis	-	-	1.66 (98)	2.78 (98)	1.38 (98)	-	1.35 (98)	-	1.49 (98)	-	-	-
Pernicious anemia	-	**1.45** (67)	2.17 (98)	3.3 (75) 5.62 (98)	2.4 (75) **3.17** (67) 4.09 (98)	**2.67** (67) 7.64 (98)	-	-	-	-	-	-
Primary biliary cirrhosis	-	**1.38** (67)	-	-	**1.66** (67)	-	-	-	-	-	**6.01** (67) [8.52] (102)	**2.06** (67)
Psoriasis	*1.40* (80) [2.02] (82)	2.80 (71)	1.78 (98) 1.97 (72) [2.16] (82)	2.97 (72) 3.01 (71) 3.36 (98)	1.45 (72)	-	-	[1.70] (82)	-	3.1 (74) 3.18 (98)	1.91 (71) 1.95 (72)	1.45 (72) 1.56 (71) *2.20* (80)

Table II. *Continued*

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Autoimmune/chronic inflammatory disease	All cancer	Focal malignancy										
		Lung	Kidney	Bladder	Brain	Endocrine	Thyroid	Breast	Ovary	Cervix	Endometrium	Prostate
Rheumatoid arthritis	1.12 (39) 1.18 (83) 1.23 (113)	1.36 (39) 1.43 (134) 1.73 (113) 2.24 (84) 2.29 (83) 3.5 (85)	1.53 (113) 2.12 (39)	1.15 (39) 1.36 (113)	-	1.62 (113)	1.41 (39)	0.87 (66) 1.21 (39)	-	0.86 (39)	0.66 (113)	1.31 (39) 1.44 (113) 1.66 (84)
Sarcoidosis	1.40 (114) 1.65* (70)	**0.60** (73) 1.71 (114)	**1.84** (73) 1.84 (114)	0.60 (114)	-	2.18 (114)	-	-	-	-	-	-
Scleroderma	1.4‡ (86) 1.55 (94) 1.99 (95) **3.15** (96) 4.2‡ (87)	2.1‡ (86) 5.9 (95) 18.6‡ (87)	-	-	-	-	-	-	-	-	-	-
Sjogren syndrome	3.25 (88)	-	-	-	-	-	-	-	-	-	-	-
Systemic lupus erythematosis	1.14 (43) 1.15 (65) 1.25 (97) 1.54 (42)	1.23 (42) 1.66 (43) 1.37 (65) 1.73 (97)	2.15 (43) 3.99 (42)	0.66 (42) 43.55 (89)	3.30 (42)	-	1.83 (43) 2.24 (42)	0.76 (65) 0.76 (43) 1.55 (42)	0.72 (42)	0.55 (43) 1.39 (42)	-	0.69 (43) 0.79 (42)
Temporal arteritis	-	-	-	-	-	-	-	-	-	-	-	-
Type 1 diabetes mellitus	1.17 (115)	-	-	-	-	-	-	-	-	1.6 (90)	2.7 (90)	-
Ulcerative colitis	1.22 (109) 1.25* (26) 1.46 (34)	-	1.50 (34)	-	-	-	-	1.25 (34)	1.88* (26)	-	-	1.14 (34)
Wegener's granulomatosis	-	-	-	-	-	-	-	-	-	-	-	-

Autoimmune/chronic inflammatory disease	All GI cancer	Focal GI malignancy									
		Buccal/Oral	Upper aero/GI tract	Esophageal	Stomach	Small bowel	Colon	Colorectal	Rectum	Anus	Liver	Pancreas
Rheumatoid arthritis	-	**0.84** (67)	1.06 (39)	1.1 (39)	-	-	0.77 (113)	0.94 (39)	0.68 (113)	-	1.16 (39) 1.32 (113)	1.08 (39)
Sarcoidosis	-	-	-	-	1.48 (114)	-	1.30 (98) 1.34 (114)	-	**1.99** (67) 2.12 (73)	3.51 (98)	1.58 (114)	-
Scleroderma	-	9.63 (94)	-	**2.86**‡ (67) 5.77 (98) 15.9 (94) 35.0‡ (87)	3.0 (87)	-	-	-	-	-	4.9‡ (87) 7.35 (103)	23.5 (87)
Sjogren syndrome	-	-	-	-	-	-	-	-	-	-	-	-
Systemic lupus erythematosis	-	-	2.03 (42) 2.86 (98)	1.63 (42)	2.08 (42)	-	1.59 (98)	0.82 (42)	-	7.18 (98)	1.83 (42) 2.60 (65) 2.70 (43)	2.00 (42)
Temporal arteritis	-	-	-	-	-	-	-	-	-	-	-	-
Type 1 diabetes mellitus	-	-	-	-	2.3 (90) 3.31 (115)	-	-	-	-	-	-	-
Ulcerative colitis	-	-	-	-	-	2.42 (34) **2.53** (67) 4.10 (98)	**2.06** (67) 2.22* (26) 3.13 (98) 3.60 (34)	1.93 (101)	1.84* (26) 1.94 (98) **2.07** (67) 2.26 (34)	-	**2.43** (67) 3.56* (26) 4.3 (34)	1.45 (34)
Wegener's granulomatosis	-	-	-	-	-	-	-	-	-	12.4 (74)	-	-

Table II. *Continued*

Table II. *Continued*

Autoimmune/chronic inflammatory disease	Focal skin malignancy									
	Skin general	Melanoma	NMSC	SCC	BCC	Appendageal	CNHL	Merkel cell	Kaposi	Other sarcomas
Addison disease	-	-	-	-	-	-	-	-	-	-
Ankylosing spondylitis	-	-	-	-	-	-	-	-	-	-
Autoimmune hemolytic anemia	-	-	-	-	-	-	-	-	-	-
Celiac disease	-	{5.0} (27)	-	-	-	-	-	-	-	-
Crohn's disease	*1.84* (106)	-	-	1.95 (33)	-	2.25 (104)	-	-	-	-
Dermatitis herpetiformis	-	-	-	-	-	-	-	-	-	-
Graves disease	-	0.73 (112)	-	-	-	-	-	-	-	2.62 (104)
Hashimoto thyroiditis	-	-	-	-	-	-	-	-	-	-
Idiopathic throbocytopenic purpura	-	-	-	-	-	-	-	-	-	-
Multiple sclerosis	-	-	-	-	-	-	-	-	-	-
Myasthenia gravis	-	-	-	-	-	-	-	-	-	-
Pernicious anemia	-	0.90 (104)	-	-	-	-	-	-	-	-
Primary biliary cirrhosis	-	-	-	-	-	-	-	-	-	-
Psoriasis	[3.10] (82)	0.32 (71) 0.87 (104)	-	2.08 (72) 2.46 (71)	-	-	3.20 (104)	-	-	-
Rheumatoid arthritis	-	1.47 (39) 1.29 (113)	0.87 (39)	1.89 (113)	-	-	-	1.39 (104)	1.65 (104)	-
Sarcoidosis	1.86* (70)	-	-	2.16 (114)	-	-	-	-	-	-
Scleroderma	-	-	-	-	**5.13** (96)	-	2.06 (104)	-	-	-
Sjogren syndrome	-	-	-	-	-	-	-	-	-	-
Systemic lupus erythematosis	1.67 (42)	0.67 (43)	-	6.43 (105)	-	-	-	-	-	-
Temporal arteritis	-	0.70 (104)	-	-	-	-	-	-	-	-
Type 1 diabetes mellitus	-	-	-	5.06 (115)	-	-	-	-	-	-
Ulcerative colitis	*1.47* (106)	-	-	-	-	-	-	-	2.76 (104)	-
Wegener's granulomatosis	-	-	-	-	-	-	-	-	-	-

Association calculations shown in normal text represent standardized incidence ratios (SIR), bolded text represents relative risk (RR), italicized text represents incidence rate ratio (IRR), underlined text represents odds ratios (OR), values in braces represent standardized morbidity ratios (SMR), text in square brackets represents hazard ratios (HR), and asterisks denote adjusted rate ratios (ARR). **Reported risk is based on incidence of cancer solely within the first year of diagnosis. †Evaluated in coincident cancer diagnosis. ‡Scleroderma risk technically based on systemic sclerosis. GI, gastrointestinal; PTC, papillary thyroid cancer; NMSC, non-melanoma skin cancer (general); SCC, squamous cell carcinoma of the skin; BCC, basal cell carcinoma; CNHL, cutaneous non-Hodgkin's lymphoma.

associations (25). Several other studies confirmed this association of celiac disease and NHL, with calculations ranging from an adjusted rate ratio (ARR) of 3.28 (26) to a standardized morbidity ratio (SMR) of 9.1 (27). T-cell NHL, specifically, was associated with celiac disease, with an odds ratio (OR) of 5.9 (28), a relative risk (RR) of 17 (29) and an SIR of 51 (30).

Other conditions demonstrating extensive associations with cancer include Crohn's disease and ulcerative colitis, collectively referred to as inflammatory bowel disease (IBD). IBD, like celiac disease, exhibited associations with gut malignancies, the primary system targeted by its inflammation. In fact, the classic pathology of IBD – granulomatous and transmural gut mucosal inflammation in Crohn's disease and primarily distal mucosal and submucosal inflammation in ulcerative colitis – may be a result of a unique milieu of inflammatory mediators experienced in each condition. This abnormal immune response appears to be the result of multifaceted immune dysregulation. For example, genetic mutations in patients with IBD have been isolated and linked to aberrancies in autophagy and eradication of antigenic material, subsequently causing abnormally high levels of inflammation. Moreover, unlike the typical immunosuppressive gut environment of unaffected people, patients with IBD appear to lose immune tolerance for normal gut flora, again creating an environment of chronic inflammation. This loss of tolerance extends to the adaptive immune systems of patients with IBD, which appear to be sensitized to self-antigens and release interleukins (IL) and interferons that eventually lead to local tissue damage. Furthermore, continued lack of immune tolerance is likely perpetuated through defects in Treg function. While Tregs typically secrete IL-10, suppressing a robust immune response, human and mouse models suggest that IBD-like pathology can develop with abnormal Tregs and impaired immune tolerance (31, 32). Resultant chronic inflammation is likely the source of increased cancer risk observed in patients with IBD. In one study, Hemminki *et al*. evaluated this relationship by following a Swedish cohort of nearly 22,000 patients with Crohn's disease for increased development of malignancy (33). This population demonstrated an SIR for cancer in general of 1.54; higher associations were calculated for small bowel carcinoma at 13.82, colon cancer at 2.93, and NHL at 2.54 (33). Ulcerative colitis, likewise, carried an elevated cancer risk based on another Swedish cohort study of approximately 28,000 patients (general cancer SIR 1.46, small bowel 2.42, colon 3.60, NHL 1.52) (34). Other studies described that the longitudinal risk of cancer and/or dysplasia in IBD increased proportionally to the number of years post-diagnosis, and was as high as 50% at 25 years (35, 36).

Strong and recurrent associations were not limited to diseases which focally target one organ or organ system. Autoimmune conditions such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), which affect multiple organ systems, had significant associations with both the development of focal types of cancer throughout the body and lymphoproliferative and hematologic malignancies. RA is an autoimmune disease that primarily affects joints and cartilage through the development of pannus, a product of inflammatory cells and mediators that transform synoviocytes within patients' joints to become locally invasive and destructive. The exact etiology of this condition remains to be fully characterized, as RA can also cause systemic manifestations affecting the skin, vasculature, heart, lungs, and peripheral nerves (37, 38). RA demonstrated many significant associations with various types of malignancies. In one study, Chen *et al*. followed a Taiwanese cohort of over 23,000 patients with RA for cancer development for an average of 5.90 years (39). Results demonstrated mildly, yet significantly elevated SIR for cancer in patients with RA. These associations included an overall association with cancer at 1.12, lung cancer at 1.36, kidney cancer at 2.12, thyroid cancer at 1.41, melanoma at 1.47, all hematologic cancer at 2.74, NHL at 3.54, Hodgkin's lymphoma at 1.76, and all leukemia at 1.48 (39). Other studies also show a broad range of cancer types associated with RA. One group, Ekstrom *et al*., utilized a Swedish database and specifically evaluated the incidence of hematologic cancer in over 75,000 patients with RA (40). Their results demonstrated significant SIR for any type of hematologic cancer at 1.07, any type of lymphoma at 2.00, NHL at 1.89, and Hodgkin's lymphoma at 3.06 (40).

Like RA, SLE has a complex multifactorial genetic and environmental etiology affecting multiple organ systems resulting in widespread loss of immune self-tolerance (41), and also showing evidence of increased cancer risk. In another Taiwanese cohort study, Chen *et al*. followed nearly 12,000 patients with SLE for cancer incidence. This study established multiple positive associations between SLE and cancer: the highest SIRs were for hematologic cancer at 4.96, NHL at 7.27, and leukemia at 2.64 (42). This study also demonstrated increased SIR for solid tumors; the risk was particularly elevated in the central nervous system at 3.30, and the kidney at 3.99 (42). Another study demonstrating multiple associations between SLE and cancer was performed by Parikh-Patel *et al*. on a Californian database of over 30,000 patients with SLE. This group was followed for an average of 5.1 years, and within that time period, associations for multiple types of cancer were identified: the SIR include 1.14 for any type of cancer, 1.66 for lung cancer, 2.15 for kidney cancer, 2.74 for NHL, 3.02 for Hodgkin's lymphoma, 2.13 for any type of leukemia, 2.96 for myelogenous leukemia, 3.26 for diffuse large B-cell lymphoma, and 2.89 for follicular lymphoma (43).

Unlike the majority of autoimmune and chronic inflammatory conditions investigated, one condition was

Table III. *Reported associations between autoimmune diseases, chronic inflammatory diseases, and hematologic malignancies.*

Autoimmune/chronic inflammatory disease	Hematologic malignancy													
	All hematologic cancer	All lymphoma	NHL	Hodgkin's lymphoma	All leukemia	Multiple myeloma	AML	CML	CLL	Diffuse large B-cell lymphoma	T-cell NHL	Marginal zone lymphoma	Follicular lymphoma	Hairy cell leukemia
Addison disease	-	-	-	-	-		-	-	-	-	-	-	-	-
Ankylosing spondylitis	-	-	-	-	-	**2.29** (76)	-	-	-	-	-	-	-	12.2† (107)
Autoimmune hemolytic anemia	8.2 (54)	-	5.0 (55) 6.5 (28) 12 (54)	-	7.0 (54)	**2.82** (76)	8.0 (54)	-	8.7 (28) **3.86** (77) 6.7 (54)	3.3 (28)	9.7 (28)	7.4 (28)	3.4 (28)	-
Celiac disease	3.3 (25)	5.9 (25)	3.28* (26) 4.7 (132) 5.35 (108) 6.3 (25) 6.6 (30) {9.1} (27)	4.6 (25) 10 (132)	-	-	-	-	-	-	5.9 (28) **17** (19) 51 (30)	3.5 (28)	-	-
Crohn's disease	-	-	1.55 (109) 2.1 (55) 2.54 (33)	-	1.57 (33)	-	-	2.80 (109)	-	-	-	-	-	10.2† (107)
Dermatitis herpetiformis	-	-	6 (110)	-	-	-	-	-	-	-	-	-	-	-
Graves disease	-	-	0.64 (112)	-	-	-	-	-	-	-	-	-	-	-
Hashimoto thyroiditis	-	-	3.0 (55)	-	-	-	-	-	-	-	-	-	-	10.3† (107)
Idiopathic thrombocytopenic purpura	3.4 (54)	-	3.4 (54)	∞ (56)	5.4 (54)	-	6.6 (54)	6.6 (54)	-	-	-	-	-	-
Multiple sclerosis	1.1 (46)	[0.76] (45)	0.6 (28)	-	-	-	-	-	-	0.4 (28)	-	-	-	-
Myasthenia gravis	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pernicious anemia	-	-	-	-	-	1.5 (28) **2.15** (76)	-	-	-	-	-	-	-	3.4† (107)
Primary biliary cirrhosis	-	-	-	∞ (56)	-	-	-	-	-	-	-	-	-	-
Psoriasis	1.4 (54) *1.81* (80)	*1.76* (80)	1.6 (54) 1.7 (55)	-	1.6 (54) *1.89* (80)	-	-	-	-	-	3.1 (28)	-	-	-
Rheumatoid arthritis	1.07 (40) 2.74 (39)	2.00 (40) 1.75 (84) 6.07 (83)	1.2 (28) **1.5** (29) 1.6 (55) 1.89 (40) 2.34 (113) 3.54 (39) 5.4 (85)	1.5 (28) *1.76* (39) 2.7 (56) 3.06 (40) 4.05 (113)	1.44 (113) 1.48 (39) 8.8 (85)	-	-	-	-	1.4 (28) **1.8** (29)	1.5 (28)	-	1.3 (28)	-

Table III. *Continued*

Table III. *Continued*

Autoimmune/chronic inflammatory disease	Hematologic malignancy													
	All hematologic cancer	All lymphoma	NHL	Hodgkin's lymphoma	All leukemia	Multiple myeloma	AML	CML	CLL	Diffuse large B-cell lymphoma	T-cell NHL	Marginal zone lymphoma	Follicular lymphoma	Hairy cell leukemia
Sarcoidosis	-	7.04* (70)	1.9 (55) 2.36 (114)	6.79 (114) 14.1 (56)	1.95 (114)	-	2.22 (114)	-	-	2.0 (28)	-	-	-	9.6†† (107)
Scleroderma	2.5‡ (86) **18.51** (96)	-	2.0‡ (55) 2.5‡ (86) **25.83** (96)	2.9 (28)	2.9‡ (86)	**2.41**‡ (76) **49.08** (96)	-	-	-	2.0‡ (28)	-	-	-	-
Sjogren syndrome	4.0 (54)	48.1 (88)	1.9 (28) 6.4 (54) 13 (111) 11.7 (55) 15.57 (92)	∞ (56)	-	37.9 (88)	-	-	-	2.0 (28)	-	6.6 (28)	-	6.1†† (107) 7.9† (107)
Systemic lupus erythematosis	2.75 (65) 4.96 (42)	-	1.5 (28) 2.74 (43) 2.86 (97) 3.3 (55) 3.64 (65) 4.2 (111) **4.6** (29) 7.27 (42) 15.37 (89)	3.02 (43) 3.5 (28) 5.8 (56)	2.13 (43) 2.64 (42)	-	2.96 (43)	-	-	3.26 (43)	2.4 (28)	2.8 (28)	2.89 (43)	7.2† (107)
Temporal arteritis	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Type 1 diabetes mellitus	-	-	-	-	3.22 (115)	-	-	-	3.6 (29)	-	-	-	-	-
Ulcerative colitis	-	-	1.52 (34)	-	-	1.65 (34)	2.15*† (26) 2.53 (109)	2.35 (109)	-	-	2.0 (28)	-	-	-
Wegener's granulomatosis	-	-	-	∞ (56)	-	-	-	-	-	-	-	-	-	-

See Table II for statistical annotation key. †Evaluated in coincident cancer diagnosis. ‡Scleroderma risk based on systemic sclerosis. ††Cancer diagnosis occurred prior to onset of inflammatory disorder. Risk values listed as ∞ were taken from studies where all patients in a group were positive for both a specific autoimmune disease and cancer. NHL, non-Hodgkin's lymphoma; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; CLL, chronic lymphoid leukemia.

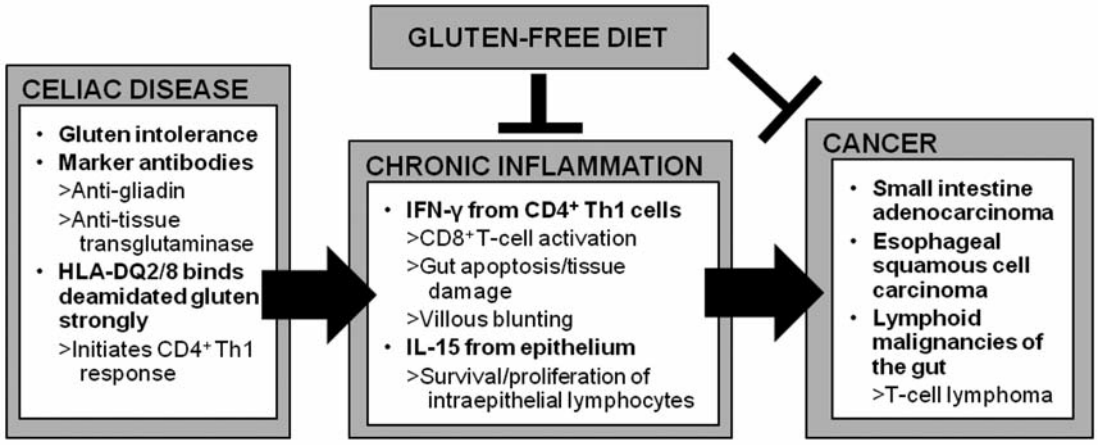

Figure 3. *Celiac disease as a paradigm for chronic inflammation predisposing patients to cancer development. Autoimmune processes and inflammation believed to contribute to cancer are shown (24, 63, 64). HLA, human lymphocyte antigen; Th1, helper T-cell type 1; IFN, interferon; IL, interleukin.*

inversely associated with cancer development in most organ systems: multiple sclerosis (MS). MS is a neurodegenerative condition where T-cell-mediated, focal autoimmune attacks against the myelin sheath surrounding nerves leads to the development of demyelinated neuronal plaques and nervous dysfunction (44). Hazard ratios (HR) were calculated in one study by Bahmanyar *et al.* of over 20,000 Swedish patients with MS to quantify the likelihood of cancer development. After an average observation period of 35.1 years, results were most notable for a decreased overall HR for cancer of 0.91, lung cancer of 0.69, ovarian cancer of 0.58, cervical cancer of 0.58, prostate cancer of 0.80, any gastrointestinal malignancy of 0.83, pancreatic cancer of 0.67, and lymphoma of 0.76 (45). This same study, however, showed an increased HR for brain neoplasms at 1.44 (45). This result is reiterated in another study by Sumelahti *et al.* investigating a smaller Finnish cohort of approximately 1,600 patients with MS evaluated to have an SIR of central nervous system malignancies of 1.3; overall association with cancer was not significant (46). The decrease in risk observed in other sites was hypothesized to be related to immunomodulatory treatment regimens or a hypothetical increase in immune surveillance concurrent with the ongoing heightened immune activity in the disease (45). The decrease in cancer risk does not appear to be conferred to first-degree relatives, and in a disease such as MS which is highly heritable, a genetic basis for the decreased risk is less likely (45).

Although other incidences were not as pervasive as the relationships of MS with types of cancer, other conditions also demonstrated occasional risk calculations suggesting a diminished risk of cancer. In the study described above by Chen *et al.* evaluating RA, the reported SIR of cervical cancer was 0.86, colorectal cancer was 0.94, and non-melanoma skin cancer was 0.87 (39). In the study by Parikh-Patel *et al.*, SLE also exhibited an SIR of 0.55 for cervical cancer, 0.76 for breast cancer, 0.69 for prostate cancer, and 0.67 for melanoma (43). Such observations may be linked to increased focal immunosurveillance in these conditions, although exact mechanisms remain unclear. Parikh-Patel *et al.* suggest that these decreases in focal risk are unlikely to be a result of increased preventative screening measures in patients with SLE, as this essential aspect of care is frequently neglected (43).

Generally, literature suggested that patients with autoimmune and chronic inflammatory disease are at higher risk for cancer development; however, as shown in Table IV, many autoimmune conditions were primarily diagnosed in patients after an initial detection of cancer. Frequent publication of case reports documenting these relationships exist, although risk calculations are largely unavailable. Certain conditions, such as *myasthenia gravis* or Lambert-Eaton myasthenic syndrome (LEMS), were so frequently observed to occur within the clinical course of malignancy that their management includes an investigation for tumors (47-50). Of the total patient population diagnosed with small cell lung cancer (SCLC), 3% show signs of LEMS (51, 52), which is characterized by antibodies targeting pre-synaptic calcium channels at the neuromuscular junction, but only the minority (30-50%) of diagnosed cases of LEMS will not eventually be associated with an established SCLC (48, 50, 53). This strong correlation has led patients with LEMS to be recommended to undergo biyearly screening to ensure a lung malignancy has not been overlooked (48). Other autoimmune conditions, such as autoimmune hemolytic anemia, may occur in a broader range of cancer types, and may be detected prior to a diagnosis of or within the course of a lymphoproliferative

malignancy (28, 54-60), notably appearing in both NHL (57, 58) and in multiple myeloma (59, 60). All conditions included in Table IV have multiple reports, suggesting the condition occurs in the setting of a pre-existing cancer, as opposed to a temporally coincidental onset of autoimmunity with cancer.

Discussion

Results presented here confirm associations between some autoimmune diseases, chronic inflammatory diseases, and cancer. The precise mechanism of the autoimmune or inflammatory disease, such as the type of cells mediating the inflammation, does not appear to affect cancer risk significantly. For example, celiac disease is primarily mediated by direct T-cell actions (24), but the characteristic immunohistologic findings in Crohn's disease are due to granulomatous macrophage responses (61, 62). Regardless of pathology, both conditions put patients at risk for the development of malignancies via ongoing tissue damage and compensatory cellular replication.

Many other autoimmune or inflammatory conditions are associated with increased risk for focal or organ-specific malignancies, and specifically, cancer of the organs targeted by the inflammatory condition. As discussed, celiac disease targets the gut and is associated with an elevated risk of gastrointestinal malignancies, although this risk may be partially reduced or eliminated in patients who eliminate gluten, the inciting antigen, from their diets (24, 27, 63, 64). Similarly, common manifestations of SLE include lupus nephritis and lupus cerebritis (41), and evidence suggests increased rates of kidney and brain cancer in these patients (42, 43). While data on the individual symptoms experienced by the patients in the reviewed studies are unavailable, it is possible that these common disease manifestations represent reduced self-tolerance and increased inflammation in these organs, in turn increasing focal cancer risk. Likewise, patients with RA frequently experience chronic lung tissue inflammation, eventually leading to interstitial lung disease, which likely predisposes to increased lung cancer risk (39).

Cancer risk due to inflammation is not limited to areas with focal organ damage. Like celiac disease, RA is defined by chronic inflammation with anti-self activity. More so than in celiac disease, RA systemically affects multiple organ systems. In particular, in the study by Chen *et al*., authors suggest that the chronic systemic inflammation and concurrent B-cell activation in patients with RA is responsible for the association with hematologic cancer (39). SLE is hypothesized to share similar systemic cancer risk factors, including increased B-cell proliferation and chronic lymphocyte activation (42). Across these conditions, an exaggerated and intolerant anti-self-tissue immune response appears to cause the damage and resulting inflammation leading to focal and systemic malignancy.

Table IV. *Cancer types frequently associated with paraneoplastic autoimmunity.*

Pre-existing cancer	Paraneoplastic autoimmune conditions (Reference)
Non-Hodgkin's lymphoma	Autoimmune hemolytic anemia (57, 58)
	Guillain-Barre syndrome (135, 136)
	Sarcoidosis (137, 138)
Hodgkin's lymphoma	Myasthenia gravis (139, 140)
Multiple myeloma	Autoimmune hemolytic anemia (59, 60)
Leukemia[1]	Guillain-Barre Syndrome (141, 142)
Thymoma	Myasthenia gravis (143, 144)
Small cell lung cancer	Guillain-Barre syndrome (145, 146)
	Lambert-Eaton syndrome (51, 147)
Sarcoma	Myasthenia gravis (148, 149)
Melanoma	Vitiligo (16, 18)

[1]Subtypes of leukemia were pooled.

Patients with MS also experience chronic inflammation begetting malignancy, as demonstrated by an increased risk of CNS cancers, the organ targeted by the disease (44). Outside of the CNS, however, MS is associated with reduced risk of cancer, potentially due to an increase in systemic anticancer immune surveillance (45). Other conditions, such as RA and SLE, also demonstrated inverse associations, although more focally in the setting of an overall increase of cancer risk (39, 42, 43, 65-67).

Conversely, multiple types of autoimmune disease have been documented during the course of a pre-existing malignancy. Vitiligo, for example, is a result of autoimmune destruction of melanocytes. It may occur as a primary autoimmune disease or secondary to malignancy, frequently malignant melanoma. Development of vitiligo in melanoma patients is hypothesized to represent a gross manifestation of the immune system's successful targeting of the cancer and loss of tolerance for self melanocytes (14). Frequently, the development of vitiligo in melanoma correlates with an improved prognosis, confirming that antigens presented on the melanoma and normal melanocytes are similar, and the immune system is responding effectively to both (14-21).

Most autoimmune diseases diagnosed during malignancy do not represent such a logical model for immune targeting, however. There is a class of conditions known as paraneoplastic syndromes which represent diseases resulting from a cross-reaction with tumor antigens. Tumor antigens that mimic proteins expressed in normal self-tissues may induce the immune system to lose tolerance for these self-proteins and inadvertently begin targeting other tissues (22, 23). This interaction may manifest as autoimmune-like conditions unrelated to the original cancer. For example, in some types of breast and ovarian cancers, a seemingly unrelated condition known as paraneoplastic cerebellar degeneration may occur. Here, the immune response to a

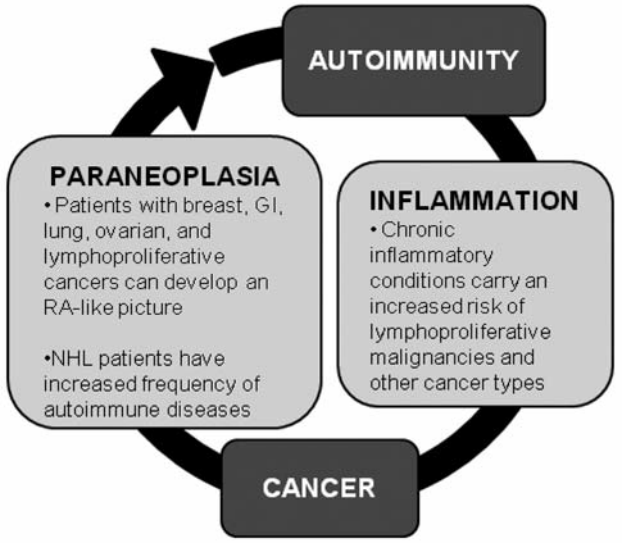

Figure 4. *A cyclic model of autoimmunity and carcinogenesis. The environment created by a chronically overactive immune response can lead to cancer development, yet it can also be a marker of developing tumor immunity. For example, rheumatoid arthritis (RA) is associated with various types of cancers. Carcinomatous polyarthritis, an RA-like condition, has been documented to develop in patients with a pre-existing cancer (23, 68). GI, gastrointestinal; NHL, non-Hodgkin's lymphoma.*

tumor expressing neural proteins also damages cerebellar tissue and results in a loss of motor control (22).

RA may also manifest in a paraneoplastic fashion. As in other autoimmune conditions, its chronic inflammatory environment likely contributes to malignant transformation of many different cell types, including those of the immune system; however, studies have noted that patients with solid tumors or lymphoproliferative disorders may develop carcinomatous polyarthritis, a paraneoplastic RA-like polyarthropathy (23, 68, 69). Autoimmune hemolytic anemia also shows a similar relationship with cancer and may develop prior to and during the course of malignancy (28, 54-60). These observations suggest that the interaction of the immune system with cancer potentially fit a cyclic model rather than a linear one (Figure 4). Such a relationship may influence the design of new immunomodulatory therapies for both inflammatory conditions and cancer.

Despite broadly observed associations between autoimmune and chronic inflammatory diseases and cancer, confounding factors may contribute to elevated risk of malignancy in these patients. For example, timing of follow-up initiation and total observation time of study patients may affect recorded cancer cases. The mean or median patient observation period length for studies reporting this statistic varied from 2.4 years (70) to 35.1 years (45), with an average of 10.5 years. The observation period did not consistently begin immediately at the time of diagnosis in all studies reviewed, as some noted that cancer risk may change during the patient's history. For example, studies by Chen *et al.* evaluating cancer risk in patients with SLE or RA showed the highest cancer SIR in the first year after diagnosis: the SIR for SLE was 193.31 (42) and that for RA was 58.96 (39). Such high values, which decreased dramatically in the following years, suggest confounding factors occurring in proximity to initial diagnosis. Because of this increased early cancer risk, several studies began collecting patient data no sooner than six months (43) to one year (25, 26, 71-77) after hospitalization. These authors reasoned that because patient information was drawn from hospitalization databases, and that in typical cases hospitalization is not required for management of either RA or SLE, there is increased likelihood that a co-existing disease (such as a malignancy) may be contributing to the acute worsening of their clinical status. Additionally, after discharge, these patients likely experienced frequent clinical evaluations, again increasing the probability of detecting subtle signs of a malignancy. Other studies, however, did not report a change in incidence and began follow-up at the time of diagnosis (27, 29, 30, 39, 40, 42, 45, 46, 54-56, 65-67, 70, 78-111). Because the majority of studies were in the latter group, when data were given in studies both for immediate and later follow-up, results reported here are from all years of follow-up combined to attempt to minimize data variability (33, 34, 112-115). For both of the studies of Chen *et al.*, overall cancer risk remained elevated eight years post-diagnosis, supporting that the significant associations remain valid and were independent of any these acute confounding factors (39, 42).

Medication usage also represents a large caveat to the associations observed between autoimmune and chronic inflammatory diseases and cancer. As mentioned above, due to the wide variety of therapies for these diseases classes, medications were not considered as a variable in this review. Some evidence, however, suggests that the specific immunomodulatory treatments used for autoimmune or chronic inflammatory disease may contribute to elevated cancer risk. Medications more frequently used in treating autoimmune and inflammatory disorders present a more complex picture, however, and associations with cancer development are controversial. Tumor necrosis factor (TNF)-α inhibitors (*e.g.* etanercept, infliximab, adalimumab) are a relatively new class of medications used for treating multiple autoimmune and inflammatory disorders, including RA, psoriasis, and Crohn's disease (116). TNF-α is an inflammatory cytokine which promotes macrophage secretion of cytotoxic enzymes and intracellular killing (32), and biologic immunomodulatory agents antagonizing TNF-α have been developed (117). As usage of this medication class has become more commonplace, concerns linking it with cancer have developed. Supporting data, however, are not

consistently nor significantly reiterated in large numbers of studies, and especially in diseases associated with increased rates of cancer development, definitively linking this drug class to cancer development has become difficult; *i.e.* the chronic inflammation necessitating the use of immunomodulatory treatments may contribute more to cancer development than the drugs themselves, and studies often do not account for disease severity when evaluating subjects (118). In addition, as the first TNF-α antagonists were only approved by the US Food and Drug Administration in 1998 (117), studies evaluating long-term effects of use are needed, particularly as some studies have noted early increases in lymphoma rates in patients treated with TNF-α inhibitors which normalize later in the treatment period (116). Other treatments for inflammatory disorders, including corticosteroids, methotrexate, and gold also do not appear to have strong associations with cancer development (111). Thus, while some immunomodulatory treatments have been linked to cancer development, given the wide variety of available treatments, frequently only recent availability, variable reports on significant associations, and the need for more long-term studies, it is likely that the associations reported in Table II and III are not due purely to a medication artifact. As an example, celiac disease supports this hypothesis, as cancer risk has been reported to decrease with the removal of the inciting antigen, gluten (24, 27, 63, 64), suggesting that cancer risk would be unrelated to medication regimen.

Future Directions

Immunomodulatory treatment options for autoimmune diseases, chronic inflammatory conditions and cancer are rapidly becoming available. In tumor immunology, the relationship between the immune system and cancer has long been a focus of study, and because of the observations with vitiligo and melanoma, one tenet in the field is that induction of an autoimmune response is essential for effective anticancer immunotherapy (119). The case of vitiligo development in melanoma supports this strategy. Induction of an autoimmune condition such as vitiligo, which is relatively benign, to treat a potentially devastating melanoma case is an appropriate compromise, but more severe side-effects should be considered while developing other anticancer immunotherapies. That is, if immunotherapy for colonic adenocarcinoma requires generating a condition such as Crohn's disease or ulcerative colitis, the adverse effects of treatment may be as life-limiting as the targeted malignancy.

Manipulating the development of immune tolerance may be more promising for treating both cancer and autoimmune diseases than simply controlling the degree of immune activity. Tumors typically create an immunosuppressive environment and migration of Tregs to the tumor further promotes its growth by influencing the adaptive immune response towards tolerance (13, 120). Origins of autoimmune and chronic inflammatory disease are frequently shown to be failures in maintaining self-tolerance. Current research is focused on breaking tolerance for anticancer immunotherapy (121) and tolerance-promoting therapies for autoimmune diseases (122). Some therapies targeting tolerance are beginning to become clinically available, such as ipilimumab for the treatment of metastatic melanoma. Ipilimumab is a monoclonal antibody towards the cytotoxic T-lymphocyte antigen (CTLA)-4 which binds B7 co-stimulatory molecules on antigen-presenting cells and indirectly causes an attenuated T-cell response and an augmented Treg response (123-125). Ipilimumab blocks the negative regulatory effects of CTLA-4, and in the setting of melanoma, allows for a more effective, non-attenuated anticancer response with improved clinical outcomes. In some patients, however, this medication generates inflammatory conditions in other previously healthy sites, particularly colitis and hypophysitis. The severity of these adverse events frequently is unrelated to concurrent antitumor immune effects (124), suggesting a persistent need for further understanding and fine-degree manipulation of the immune tolerance spectrum.

As demonstrated by the many examples above, an understanding of the subtle differences in immune interactions which lead to autoimmune diseases, chronic inflammatory conditions, and cancer is becoming essential as immunotherapy is becoming a common treatment modality. Specifically, the group of treatments which induce or inhibit immune tolerance may represent a strategy to address what may appear to be a cyclic relationship between these conditions, while ideally avoiding severe adverse effects. As the relationships between these conditions become more apparent through longitudinal study, a thorough understanding of the defining mechanisms taking place will be crucial for effective therapy development and disease management.

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