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Immune-Mediated Diseases Associated With Cancer Risks

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IMPORTANCE Immune regulation is important for carcinogenesis; however, the cancer risk profiles associated with immune-mediated diseases need further characterization.

OBJECTIVE To assess the prospective association of 48 immune-mediated diseases with the risk of total and individual cancers and the prospective association of organ-specific immune-mediated diseases with the risk of local and extralocal cancers.

DESIGN, SETTING, AND PARTICIPANTS This prospective cohort study used data from the UK Biobank cohort study on adults aged 37 to 73 years who were recruited at 22 assessment centers throughout the UK between January 1, 2006, and December 31, 2010, with follow-up through February 28, 2019.

EXPOSURES Immune-mediated diseases.

MAIN OUTCOMES AND MEASURES The association of immune-mediated diseases with risk of cancer was assessed with multivariable hazard ratios (HRs) and 95% CIs after adjusting for various potential confounders using time-varying Cox proportional hazards regression. Heterogeneity in the associations of organ-specific immune-mediated diseases with local and extralocal cancers was assessed using the contrast test method.

RESULTS A total of 478 753 participants (mean [SD] age, 56.4 [8.1] years; 54% female) were included in the study. During 4 600 460 person-years of follow-up, a total of 2834 cases of cancer were documented in 61 496 patients with immune-mediated diseases and 26 817 cases of cancer in 417 257 patients without any immune-mediated diseases (multivariable HR, 1.08; 95% CI, 1.04-1.12). Five of the organ-specific immune-mediated diseases were significantly associated with higher risk of local but not extralocal cancers: asthma (HR, 1.34; 95% CI, 1.14-1.56), celiac disease (HR, 6.89; 95% CI, 2.18-21.75), idiopathic thrombocytopenic purpura (HR, 6.94; 95% CI, 3.94-12.25), primary biliary cholangitis (HR, 42.12; 95% CI, 20.76-85.44), and autoimmune hepatitis (HR, 21.26; 95% CI, 6.79-66.61) ($P < .002$ for heterogeneity). Nine immune-mediated diseases were associated with an increased risk of cancers in the involved organs (eg, asthma with lung cancer [HR, 1.34; 95% CI, 1.14-1.57; $P < .001$] and celiac disease with small intestine cancer [HR, 6.89; 95% CI, 2.18-21.75; $P = .001$]); 13 immune-mediated diseases were associated with an increased risk of cancer in the near organs (eg, Crohn disease with liver cancer: [HR, 4.01; 95% CI, 1.65-9.72; $P = .002$]) or distant organs (eg, autoimmune hepatitis with tongue cancer [HR, 27.75; 95% CI, 3.82-199.91; $P = .001$]) or in different systems (eg, idiopathic thrombocytopenic purpura with liver cancer [HR, 11.96; 95% CI, 3.82-37.42; $P < .001$]).

CONCLUSIONS AND RELEVANCE In this cohort study, immune-mediated diseases were associated with an increased risk of total cancer. Organ-specific immune-mediated diseases had stronger associations with risk of local cancers than extralocal cancers. The associations for individual immune-mediated diseases were largely organ specific but were also observed for some cancers in the near and distant organs or different systems. Our findings support the role of local and systemic immunoregulation in cancer development.

Invited Commentary

Supplemental content

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Inflammation plays a pivotal role in carcinogenesis. Recent breakthroughs in cancer immunotherapy have markedly advanced our understanding about the importance of immunoregulation in cancer development. Specific mechanisms of immunoregulation in tumorigenesis have been elucidated, such as tumor-promoting inflammation, T_H17 and regulatory T-cell (Treg)–mediated suppression of immune surveillance, inhibition of T_H1 immunity, and local and distant tumorigenesis regulated by microbiota via alterations in the inflammatory and metabolic circuitry.[1]

Immune-mediated diseases constitute a clinically heterogeneous group of disorders, affecting up to 10% of the population worldwide.[2,3] Several of the aforementioned immune mechanisms for cancer are also implicated in immune-mediated diseases, such as inflammation-promoting T_H17 dominance, dysfunctional Treg surveillance, and microbiota cross talk between colonized and distant organs.[4,5] Several immune-mediated diseases have been associated with increased risk of cancer in the involved organs, such as inflammatory bowel diseases and colorectal cancer,[6] primary sclerosing cholangitis and hepatobiliary cancer,[7] and celiac disease and small intestine cancer.[8] These findings suggest a local carcinogenic effect of immune dysregulation. However, a recent study[9] found an association of certain immune-mediated diseases with higher risk of cancer in the distant organs, such as Crohn disease with extracolonic cancer and ulcerative colitis with hepatobiliary cancer. Rheumatoid arthritis as a systemic disease has been associated with a higher risk of lymphoma and lung cancer and a lower risk of breast, colorectal, and prostate cancers.[10,11] These findings suggest that some immune-mediated diseases may be associated with cancer risk in the distant organs or systemically beyond local organs.

To our knowledge, no studies have examined the association of organ-specific immune-mediated diseases with the risk of local and extralocal cancers. The cancer risk profiles for individual immune-mediated diseases need further characterization. Moreover, although immune-mediated diseases and cancer share some similar environmental triggers,[12] most prior studies[7,13] did not adjust for the lifestyle risk factors that may confound the associations. In addition, previous studies[7,13] did not assess the less common immune-mediated diseases associated with cancer risk.

We comprehensively assessed the prospective association of 48 immune-mediated diseases with risk of total and individual cancers in the UK Biobank. We also tested the organ specificity of the associations by mapping each organ-specific immune-mediated disease with risk of local and extralocal cancers.

Key Points

Question What are the profiles of cancer risk associated with immune-mediated diseases?

Findings In this cohort study of 478 753 participants, immune-mediated diseases were associated with an increased risk of total cancer. Organ-specific immune-mediated diseases had stronger associations with risk of local cancers than extralocal cancers, and many immune-mediated diseases were associated with increased risk of cancer in the involved organs and in the near and distant organs or different systems.

Meaning The findings suggest that immune-mediated diseases are associated with risk of cancer at the local and systemic levels, supporting the role of local and systemic immunoregulation in carcinogenesis.

Methods

Study Participants

This cohort study was a post hoc analysis of the UK Biobank study, a prospective cohort study that aimed to investigate the genetic, lifestyle, and environmental causes of a range of diseases.[14] Between January 1, 2006, and December 31, 2010, a total of 502 536 adults aged 37 to 73 years were recruited at 22 assessment centers throughout the UK. All participants were registered with the UK National Health Service. At the recruitment visit, participants completed a self-administered touchscreen questionnaire on sociodemographic characteristics, lifestyle exposures, medical history, and medication use and underwent physical measurements. The *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) was used to record disease diagnoses. For the current study, we excluded participants who withdrew informed consent (n = 30) and those who had prevalent cancer at recruitment (n = 23 753). A total of 478 753 participants were included. All participants provided written informed consent. All data were deidentified. The UK Biobank received ethical approval from the UK National Health Service, National Research Ethics Service North West, the National Information Governance Board for Health and Social Care in England and Wales, and the Community Health Index Advisory Group in Scotland. In addition, an independent ethics and governance council was formed to oversee its continued adherence to the ethics and governance framework. The current study was approved by the UK Biobank. Additional ethical approval and other details are provided in the eMethods in the Supplement. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Ascertainment of Immune-Mediated Diseases

We identified a total of 48 immune-mediated diseases and compared cancer risk between individuals with and without any of these diseases. For analyses of individual immune-mediated diseases, we focused on the 27 diseases with at least 100 affected individuals and at least 10 cancer cases among the affected individuals (eTable 1 in the Supplement). Among the diseases, we assessed 12 organ-specific diseases for their associations with local or extralocal cancer that was diagnosed in at least 1 participant. The diagnosis date was the date when the *ICD-10* code was first recorded in participants' inpatient records. We required the immune-mediated disease diagnosis to be present at least 12 months before the cancer diagnosis.

Outcome Ascertainment

The outcome of interest was the incidence of total and individual cancers. Incident cancer cases within the UK Biobank were identified by *ICD-10* codes through linkage to the national cancer registry (C01-C97). Total cancers included all cancers except nonmelanoma skin cancer (C44). For analysis of individual cancers, we restricted to those with at least 100 events (eTable 2 in the Supplement).

Statistical Analysis

All participants were followed up from the date of recruitment until that of cancer diagnosis, death, loss to follow-up, or the end of the study period (February 28, 2019), whichever occurred first. A total of 1253 participants were lost to follow-up, and thus, 99.7% completed the study. Individuals with either prevalent immune-mediated diseases reported at baseline enrollment or incident diseases reported during follow-up were classified as the exposure group. For incident cases, patients were considered to have no immune-mediated disease until the date of the first reported diagnosis during follow-up.

We calculated hazard ratios (HRs) and 95% CIs of total and individual cancers using time-varying Cox proportional hazards regression with age as the time scale. Model 1 was adjusted for age at recruitment, sex, and ethnicity. Model 2 was further adjusted for a set of a priori determined cancer risk factors that may be associated with immune-mediated diseases, including socioeconomic status (Townsend deprivation score), educational level, total physical activity, body mass index (BMI), waist-to-hip ratio, height, smoking status and intensity, alcohol use, consumption of processed meat and oily fish, family history of cancer, and regular use of aspirin and vitamin supplements. Sensitivity analysis of medications for immune-mediated diseases and histologic finding-specific analysis are described in the eMethods in the Supplement.

For the organ-specific immune-mediated diseases, we calculated the *P* value for heterogeneity in the associations of immune-mediated diseases with local and extralocal cancers using the contrast test method based on a fully unconstrained approach developed in the competing risks framework using a cause-specific proportional hazards model.[15] To account for multiple testing, we performed Bonferroni correction for the primary analysis on the associations of the 27 individual immune-mediated diseases with total cancer risk and considered $\alpha = .05/27 = .002$ as statistically significant. We did not conduct the correction for secondary analyses on individual cancers, which were considered exploratory, and interpreted the results with caution. SAS software, version 9.4 (SAS Institute Inc) was used for all analyses. All statistical tests were 2-sided.

Results

Characteristics of the Study Population

A total of 478 753 participants (mean [SD] age, 56.4 [8.1] years; 54% female) were assessed in this cohort study. Most participants were White (95%), and 61 496 (13%) had at least 1 immune-mediated disease (**Table 1**). Compared with participants without immune-mediated diseases, participants with immune-mediated diseases were more likely to have lower socioeconomic status, higher BMI, and lower physical activity; smoke; consume processed meat and vitamins; and use aspirin. They were less likely to have a college or university education and to consume alcohol (Table 1).

Any Immune-Mediated Diseases and Risk of Total Cancer

During a total of 4 600 460 person-years and a median of 10.0 (IQR, 9.2-10.7) years of follow-up, we documented 2834 cases of cancer in participants with immune-mediated diseases and 26 817 cases in those without immune-mediated diseases. Overall, immune-mediated diseases were associated with total cancer risk after multivariable adjustment (model 2: HR, 1.08; 95% CI, 1.04-1.12) (**Figure 1**). Further adjustment for medication use did not substantially alter the results (HR, 1.06; 95% CI, 1.01-1.10), and self-reported medication use at recruitment was not associated with cancer risk (eTables 3 and 4 in the Supplement).

Individual Immune-Mediated Diseases and Risk of Total Cancer

Ulcerative colitis was significantly associated with an increased risk of total cancer, with a multivariable-adjusted HR of 1.33 (95% CI, 1.17-1.51). Asthma (HR, 1.06; 95% CI, 1.01-1.12) and primary biliary cholangitis (HR, 1.74; 95% CI, 1.10-2.76) were associated with an increased risk of total cancer (Figure 1).

Any Immune-Mediated Disease and Risk of Individual Cancers

For individual cancers, participants with any immune-mediated disease were at higher risk of developing lung cancer (multivariable-adjusted HR, 1.36; 95% CI, 1.20-1.53), lymphoma (multivariable-adjusted HR, 1.49; 95% CI, 1.26-1.75), and liver cancer (HR, 1.75; 95% CI, 1.30-2.36) (**Figure 2**). We further assessed the association of any immune-mediated disease with risk of cancers according to histologic findings and did not find any histologic finding–specific differences (eTable 5 in the Supplement).

Organ-Specific Immune-Mediated Diseases and Risk of Local and Extralocal Cancers

Five of the organ-specific immune-mediated diseases were significantly associated with the increased risk of local cancers, but not extralocal cancers: asthma with lower airway cancer (HR, 1.34; 95% CI, 1.14-1.56), celiac disease with small intestine cancer (HR, 6.89; 95% CI, 2.18-21.75), idiopathic thrombocytopenic purpura with hematologic cancer (HR, 6.94; 95% CI, 3.94-12.25), primary biliary cholangitis with hepatobiliary cancer (HR, 42.12; 95% CI, 20.76-85.44), and autoimmune hepatitis with hepatobiliary cancer (HR, 21.26; 95% CI, 6.79-66.61) ($P < .001$ for all comparisons; $P < .002$ for heterogeneity). In contrast, ulcerative colitis was significantly associated with higher risk of colorectal cancer and extracolorectal cancer, with a stronger association for colorectal (HR, 1.73; 95% CI, 1.26-2.39) than extracolorectal cancer (HR, 1.30; 95% CI, 1.13-1.49) (**Table 2**).

Table 1. Age-Standardized Characteristics of Study Participants at Baseline[a]

Characteristic	Participants with immune-mediated diseases (n = 61 496)	Participants without immune-mediated diseases (n = 417 257)
Age at recruitment, mean (SD), y	57.6 (8.0)	56.2 (8.1)
Sex, %		
Female	54	54
Male	46	46
Socioeconomic status (Townsend deprivation score), mean (SD)	−0.9 (3.3)	−1.4 (3.1)
Height, mean (SD), cm	168.0 (9.4)	168.6 (9.2)
BMI, mean (SD)	28.5 (5.5)	27.3 (4.7)
Waist-to-hip ratio, mean (SD)	0.9 (0.1)	0.9 (0.1)
Total physical activity (MET), mean (SD), h/wk	42.1 (46.5)	44.6 (45.1)
Race and ethnicity, %		
Asian	3	2
Black	2	2
Mixed	1	1
White	93	94
Other[b]	1	1
College or university education, %	27	33
Smoking status, %		
Never	51	55
Previous	37	34
Current	12	10
Unknown	1	1
Alcohol consumption frequency, %		
None	12	7
Special occasions only	15	11
1-3 Times a month	12	11
1-2 Times a week	25	26
3-4 Times a week	20	24
Daily or almost daily	18	21
Unknown	0	0
Family history of cancer, %	35	35
Oily fish, occasions per week, %		
Never	13	11
<1	32	33
1	35	38
2-4	17	17
5-6	1	1
≥7	0	0
Unknown	1	1
Processed meat, occasions per week, %		
Never	9	9
<1	29	31
1	29	29
2-4	29	27
5-6	4	3
≥7	1	1
Unknown	1	0
Aspirin use, %	18	13
Vitamin supplement, %	35	31
Overall health status, %		
Excellent	7	18
Good	46	60
Fair	34	19
Poor	13	3
Unknown	0	0

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); MET, metabolic equivalents.

[a] All variables are age-standardized except age.

[b] UK Biobank did not define "other" racial and ethnic groups.

Individual Immune-Mediated Diseases and Risk of Individual Cancers

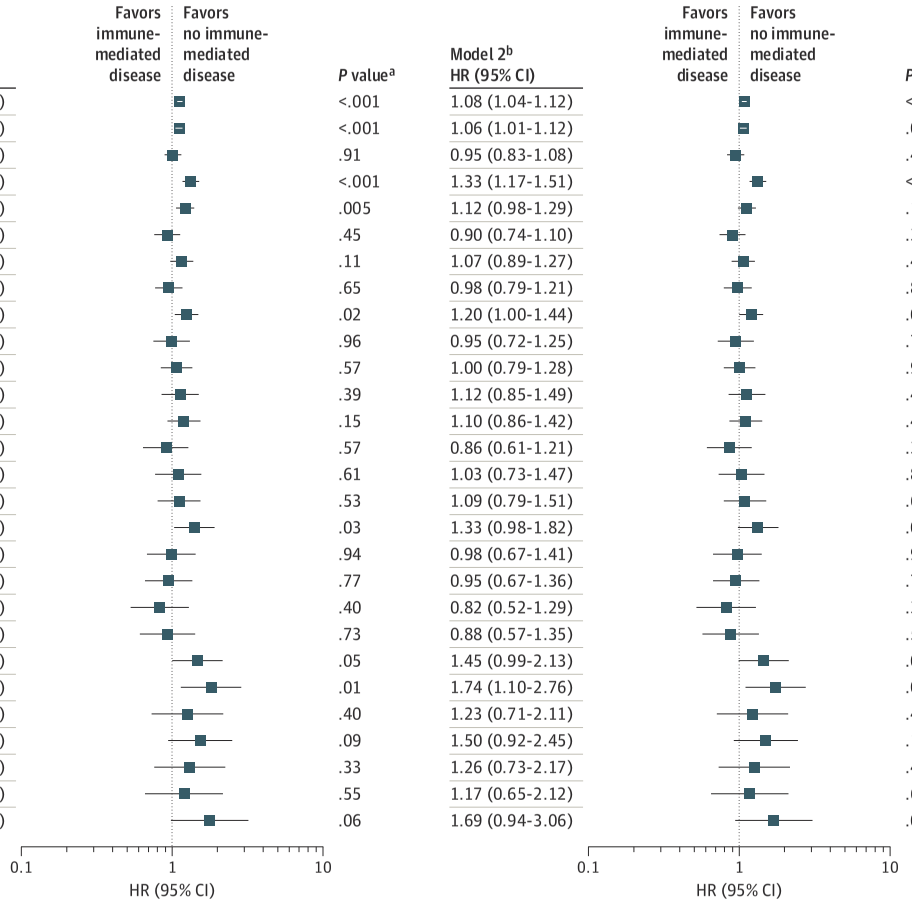
Figure 3 shows the results for the site-specific analysis associating individual immune-mediated diseases with individual cancers (detailed results are presented in eTables 6 and 7 in the Supplement). Seven immune-mediated diseases were significantly associated with an increased risk of cancer in the involved organs, such as asthma with lung cancer (HR, 1.34; 95% CI, 1.14-1.57) and celiac disease with small intestine cancer (HR, 6.89; 95% CI, 2.18-21.75). The HRs ranged from 1.34 (95% CI, 1.14-1.57) to 62.42 (95% CI, 29.14-133.74) ($P < .002$). In addition, 2 associations with cancers in the involved organs were found for sicca syndrome with small intestine (HR, 8.49; 95% CI, 1.18-61.32) and mouth cancers (HR, 13.59; 95% CI, 1.86-99.09) and Guillain-Barré syndrome with soft tissue cancer (HR, 11.17; 95% CI, 1.56-79.80).

Thirteen immune-mediated diseases were associated with an increased risk of cancer in the near or distant organs or different systems. Among them, 2 were associated with increased risk of cancer in the near organs (Crohn disease with liver cancer [HR, 4.01; 95% CI, 1.65-9.72] and ulcerative colitis with liver cancer [HR, 2.59; 95% CI, 1.15-5.81]); 2 were associated with cancer in the distant organs (autoimmune hepatitis with tongue cancer [HR, 27.65; 95% CI, 3.82-199.91] and esophageal cancer [HR, 9.28; 95% CI, 1.31-65.94] and ulcerative colitis with tongue cancer [HR, 3.49; 95% CI, 1.29-9.43]). Twelve immune-mediated diseases were associated with cancers in different systems, such as idiopathic thrombocytopenic purpura with liver cancer (HR, 11.96; 95% CI, 3.82-37.42), bullous disorders with laryngeal cancer (HR, 26.23; 95% CI, 3.62-190.15), Graves disease or autoimmune thyroiditis with soft tissue cancer (HR, 9.19; 95% CI, 2.93-28.81), and ulcerative colitis with prostate cancer (HR, 1.45; 95% CI, 1.13-1.85).

Among all cancers, lymphoma demonstrated an extensive association with immune-mediated diseases. The HR ranged from 2.01 (95% CI, 1.34-3.01) for rheumatoid arthritis to 7.72 (95% CI, 3.67-16.23) for idiopathic thrombocytopenic purpura. Rheumatoid arthritis was associated with an increased risk of lung cancer (HR, 1.71; 95% CI, 1.28-2.28) and

Figure 1. Total Cancers Associated With Immune-Mediated Diseases

Immune-mediated disease	No. of participants with the disease	Total cancer cases, No.		Model 1[a] HR (95% CI)	*P* value[a]	Model 2[b] HR (95% CI)	*P* value[b]
		Immune-mediated disease	No immune-mediated disease				
Any	61496	2834	26817	1.12 (1.08-1.17)	<.001	1.08 (1.04-1.12)	<.001
Asthma	33269	1462	28189	1.11 (1.05-1.17)	<.001	1.06 (1.01-1.12)	.03
Rheumatoid arthritis	5939	243	29408	1.01 (0.89-1.15)	.91	0.95 (0.83-1.08)	.42
Ulcerative colitis	3941	251	29400	1.33 (1.17-1.51)	<.001	1.33 (1.17-1.51)	<.001
Diabetes (type 1)	3556	211	29440	1.22 (1.06-1.40)	.005	1.12 (0.98-1.29)	.11
Rheumatic fever or rheumatic heart diseases	3171	98	29553	0.93 (0.76-1.13)	.45	0.90 (0.74-1.10)	.32
Psoriasis	2979	127	29524	1.15 (0.97-1.38)	.11	1.07 (0.89-1.27)	.47
Celiac disease	2273	91	29560	0.95 (0.77-1.17)	.65	0.98 (0.79-1.21)	.85
Crohn disease	2157	117	29534	1.24 (1.04-1.49)	.02	1.20 (1.00-1.44)	.05
Polymyalgia rheumatica	1659	52	29599	0.99 (0.75-1.31)	.96	0.95 (0.72-1.25)	.73
Multiple sclerosis	1610	68	29583	1.07 (0.84-1.36)	.57	1.00 (0.79-1.28)	.98
Allergic rhinitis	1636	49	29602	1.13 (0.85-1.50)	.39	1.12 (0.85-1.49)	.41
Rheumatism, unspecified	1174	62	29589	1.20 (0.93-1.54)	.15	1.10 (0.86-1.42)	.46
Psoriatic or enteropathic arthropathies	949	32	29619	0.91 (0.64-1.28)	.57	0.86 (0.61-1.21)	.38
Graves disease or autoimmune thyroiditis	823	34	29617	1.10 (0.77-1.56)	.61	1.03 (0.73-1.47)	.86
Ankylosing spondylitis	787	36	29615	1.11 (0.80-1.54)	.53	1.09 (0.79-1.51)	.60
Necrotizing vasculopathies[c]	772	41	29610	1.40 (1.03-1.91)	.03	1.33 (0.98-1.82)	.07
Sarcoidosis	737	29	29622	0.99 (0.68-1.43)	.94	0.98 (0.67-1.41)	.90
Lichen planus	716	30	29621	0.95 (0.66-1.36)	.77	0.95 (0.67-1.36)	.79
Sicca syndrome	702	19	29632	0.82 (0.53-1.29)	.40	0.82 (0.52-1.29)	.39
Systemic lupus erythematosus	611	22	29629	0.93 (0.61-1.42)	.73	0.88 (0.57-1.35)	.55
Idiopathic thrombocytopenic purpura	459	29	29622	1.47 (1.00-2.16)	.05	1.45 (0.99-2.13)	.06
Primary biliary cholangitis	268	18	29633	1.81 (1.14-2.87)	.01	1.74 (1.10-2.76)	.02
Myositis	263	14	29637	1.26 (0.73-2.18)	.40	1.23 (0.71-2.11)	.46
Guillain-Barré syndrome	252	16	29635	1.53 (0.94-2.50)	.09	1.50 (0.92-2.45)	.10
Myasthenia gravis	231	14	29637	1.31 (0.76-2.25)	.33	1.26 (0.73-2.17)	.41
Bullous disorders	229	11	29640	1.20 (0.66-2.17)	.55	1.17 (0.65-2.12)	.60
Autoimmune hepatitis	203	12	29639	1.77 (0.98-3.20)	.06	1.69 (0.94-3.06)	.08



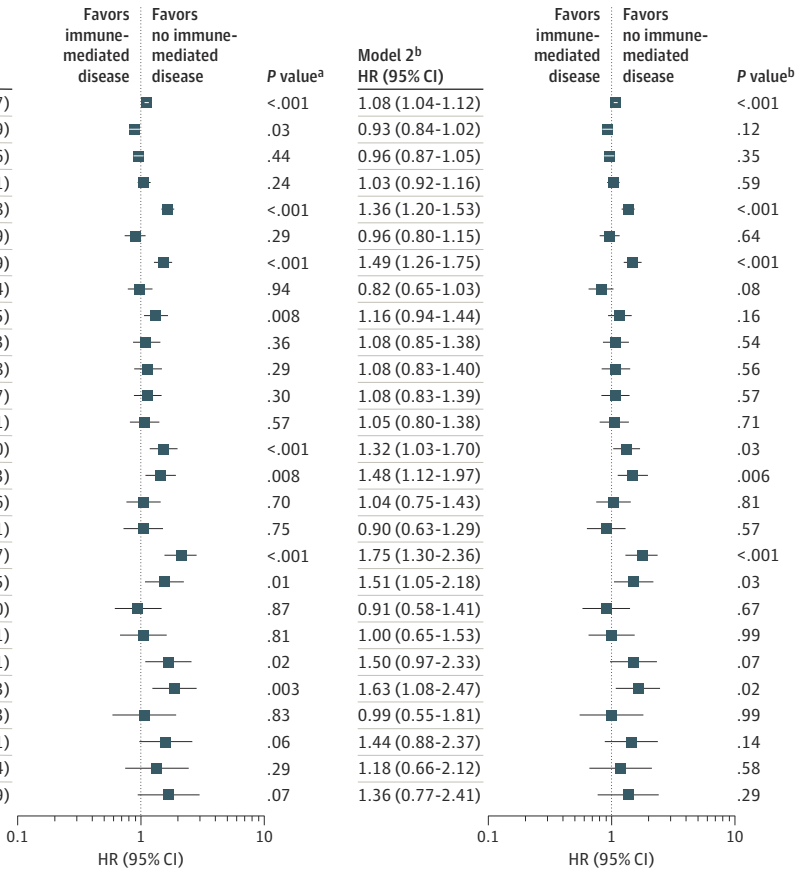
[a] Model 1 was adjusted for age at recruitment, sex, and ethnicity.

[b] Model 2 was further adjusted for socioeconomic status (Townsend deprivation score), educational level, total physical activity, body mass index, waist-to-hip ratio, height, smoking status and intensity, alcohol status and consumption frequency, frequency of processed meat consumption, frequency of oily fish consumption, family history of cancer, vitamin supplements, and regular use of aspirin.

[c] Necrotizing vasculopathies except vasculitis limited to the skin.

Figure 2. Site-Specific Cancers Associated With Immune-Mediated Diseases

Cancer type	Cancer cases, No.		Model 1[a] HR (95% CI)	P value[a]	Model 2[b] HR (95% CI)	P value[b]
	Immune-mediated disease	No immune-mediated disease				
Any	2834	26817	1.12 (1.08-1.17)	<.001	1.08 (1.04-1.12)	<.001
Prostate	446	5781	0.90 (0.81-0.99)	.03	0.93 (0.84-1.02)	.12
Breast	522	5444	0.96 (0.88-1.06)	.44	0.96 (0.87-1.05)	.35
Colorectal	310	3139	1.07 (0.95-1.21)	.24	1.03 (0.92-1.16)	.59
Lung	326	1974	1.67 (1.48-1.88)	<.001	1.36 (1.20-1.53)	<.001
Melanoma	132	1597	0.91 (0.76-1.09)	.29	0.96 (0.80-1.15)	.64
Lymphoma	176	1241	1.53 (1.30-1.79)	<.001	1.49 (1.26-1.75)	<.001
Uterine	85	858	0.99 (0.79-1.24)	.94	0.82 (0.65-1.03)	.08
Kidney	97	789	1.33 (1.08-1.65)	.008	1.16 (0.94-1.44)	.16
Leukemia	75	693	1.12 (0.88-1.43)	.36	1.08 (0.85-1.38)	.54
Bladder	68	631	1.15 (0.89-1.48)	.29	1.08 (0.83-1.40)	.56
Pancreatic	65	599	1.14 (0.89-1.47)	.30	1.08 (0.83-1.39)	.57
Ovarian	61	556	1.08 (0.83-1.41)	.57	1.05 (0.80-1.38)	.71
Esophageal	72	503	1.56 (1.22-2.00)	<.001	1.32 (1.03-1.70)	.03
Brain	58	437	1.46 (1.11-1.93)	.008	1.48 (1.12-1.97)	.006
Multiple myeloma	41	408	1.06 (0.77-1.46)	.70	1.04 (0.75-1.43)	.81
Stomach	35	346	1.06 (0.74-1.51)	.75	0.90 (0.63-1.29)	.57
Liver	55	269	2.14 (1.59-2.87)	<.001	1.75 (1.30-2.36)	<.001
Soft tissue	34	237	1.57 (1.10-2.25)	.01	1.51 (1.05-2.18)	.03
Mesothelioma	26	240	0.97 (0.62-1.50)	.87	0.91 (0.58-1.41)	.67
Thyroid	24	245	1.05 (0.69-1.61)	.81	1.00 (0.65-1.53)	.99
Tongue	27	163	1.69 (1.10-2.61)	.02	1.50 (0.97-2.33)	.07
Biliary duct	28	142	1.88 (1.25-2.83)	.003	1.63 (1.08-2.47)	.02
Tonsil	12	137	1.07 (0.59-1.93)	.83	0.99 (0.55-1.81)	.99
Small intestine	19	125	1.60 (0.98-2.61)	.06	1.44 (0.88-2.37)	.14
Mouth	11	109	1.36 (0.76-2.44)	.29	1.18 (0.66-2.12)	.58
Laryngeal	14	99	1.70 (0.96-2.99)	.07	1.36 (0.77-2.41)	.29



[a] Model 1 was adjusted for age at recruitment, sex, and ethnicity.

[b] Model 2 was further adjusted for socioeconomic status (Townsend deprivation score), educational level, total physical activity, body mass index, waist-to-hip ratio, height, smoking status and intensity, alcohol status and consumption frequency, frequency of processed meat consumption, frequency of oily fish consumption, family history of cancer, vitamin supplements, and regular use of aspirin.

lym\phoma (HR, 2.01; 95% CI, 1.34-3.01) but a decreased risk of prostate (HR, 0.62; 95% CI, 0.41-0.94) and breast (HR, 0.64; 95% CI, 0.46-0.89) cancers. Necrotizing vasculopathies as a systemic disease was significantly associated with an increased risk of multiple myeloma (HR, 7.98; 95% CI, 2.97-21.43). Type 1 diabetes was associated with an increased risk of liver (HR, 2.82; 95% CI, 1.43-5.56), esophageal (HR, 2.13; 95% CI, 1.13-4.02), and tonsil (HR, 3.57; 95% CI, 1.11-11.46) cancers but a decreased risk of prostate cancer (HR, 0.67; 95% CI, 0.46-0.97).

Discussion

In this large prospective cohort study, we found that any immune-mediated disease was associated with a modestly increased risk of total cancer after adjusting for common cancer risk factors. Although organ-specific immune-mediated diseases had stronger positive associations with risk of local cancers than extralocal cancers, several immune-mediated diseases were associated with an increased risk of cancers in the near or distant organs or different systems. Some systemic immune-mediated diseases had a positive association with risk of some cancers but a negative association with risk of other cancers. These findings may provide insight into the local and systemic effect of immune-mediated disease in the development of cancer.

To our knowledge, the current study represents the first comprehensive effort to dissect various individual immune-mediated diseases associated with cancer risk. We found that ulcerative colitis, asthma, and primary biliary cholangitis were associated with an increased risk of total cancer. These findings are consistent with prior studies.[16-18] For example, a national cohort study[16] in Sweden found an association of asthma with a 19% increased risk of total cancer. Ulcerative colitis was associated with a 40% higher risk of total cancer, mainly colorectal and hepatobiliary cancers.[17] Patients with primary biliary cholangitis had double the risk of total cancer and approximately 40 times higher risk of hepatobiliary cancer.[18]

Furthermore, we reported, for the first time to our knowledge, that organ-specific immune-mediated diseases were more strongly associated with higher risk of local cancers than

Table 2. Local and Extralocal Cancers Associated With Organ-Specific Immune-Mediated Diseases[a]

Immune-mediated disease, cancer outcome	Cancer cases, No.	Hazard ratio (95% CI)	*P* value	*P* value for heterogeneity
Asthma				
Lower airway cancer[b]	178	1.34 (1.14-1.56)	<.001	<.002
Extra-lower airway cancer	1292	1.03 (0.97-1.09)	.38	
Ulcerative colitis				
Colorectal cancer	39	1.73 (1.26-2.39)	<.001	.10
Extracolorectal cancer	217	1.30 (1.13-1.49)	<.001	
Psoriasis				
Melanoma	8	1.35 (0.67-2.71)	.40	.48
Extramelanoma	119	1.04 (0.87-1.25)	.65	
Crohn disease				
Mouth to anal cancer	27	1.34 (0.92-1.96)	.13	.46
Extra-mouth to anal cancer	91	1.14 (0.93-1.40)	.21	
Inflammatory bowel disease				
Colorectal cancer	48	1.54 (1.15-2.05)	.004	.19
Extracolorectal cancer	295	1.25 (1.11-1.40)	<.001	
Celiac disease				
Small intestine cancer	3	6.89 (2.18-21.75)	.001	<.001
Extra-small intestine cancer	89	0.96 (0.78-1.19)	.70	
Allergic rhinitis				
Upper airway cancer	1	1.08 (0.15-7.70)	.94	.97
Extra-upper airway cancer	48	1.12 (0.84-1.49)	.43	
Multiple sclerosis				
Central nervous cancer	1	0.80 (0.11-5.71)	.83	.82
Extra-central nervous cancer	67	1.01 (0.79-1.28)	.97	
Graves disease or autoimmune thyroiditis				
Thyroid cancer	1	2.76 (0.39-19.68)	.31	.32
Extrathyroid cancer	33	1.00 (0.70-1.43)	>.99	
Idiopathic thrombocytopenic purpura				
Hematologic cancer	13	6.94 (3.94-12.25)	<.001	<.001
Extrahematologic cancer	16	0.87 (0.53-1.45)	.59	
Primary biliary cholangitis				
Hepatobiliary cancer	7	42.12 (20.76-85.44)	<.001	<.001
Extrahepatobiliary cancer	11	1.07 (0.59-1.93)	.83	
Autoimmune hepatitis				
Hepatobiliary cancer	3	21.26 (6.79-66.61)	<.001	<.001
Extrahepatobiliary cancer	9	1.25 (0.63-2.50)	.53	

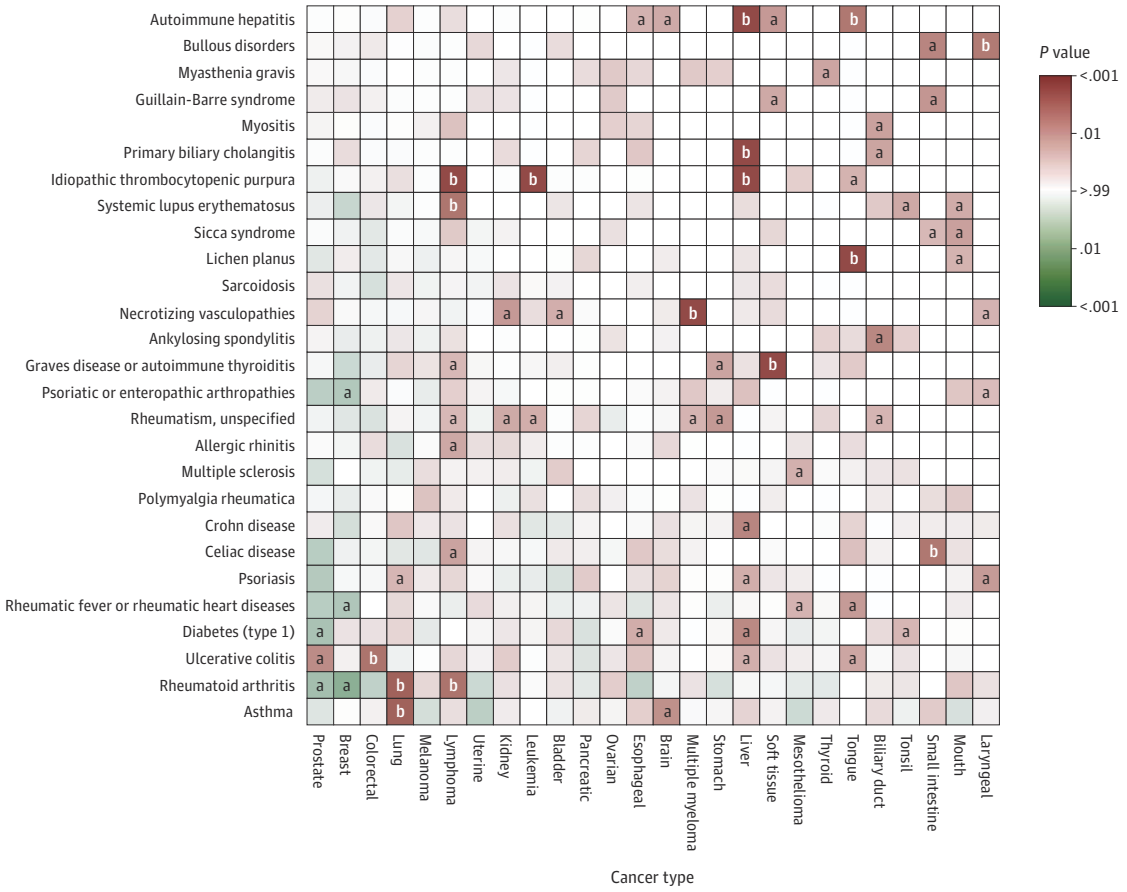
[a] A Cox proportional hazards regression model was adjusted for age at recruitment, sex, ethnicity, socioeconomic status (Townsend deprivation score), educational level, total physical activity, body mass index, waist-to-hip ratio, height, smoking status and intensity, alcohol status and consumption frequency, frequency of processed meat consumption, frequency of oily fish consumption, family history of cancer, vitamin supplements, and regular use of aspirin.

[b] Malignant neoplasm of larynx, trachea, bronchus, and lung.

extralocal cancers. We identified 7 immune-mediated diseases that were significantly associated with increased risk of cancer in the involved organs. These findings suggest an important role of a local carcinogenic effect of immune dysregulation. Similar associations with local cancer risk have been reported in previous studies of asthma,[19] ulcerative colitis,[6] primary biliary cholangitis,[7] celiac disease,[8] autoimmune hepatitis,[20] idiopathic thrombocytopenic purpura,[21] and lichen planus.[22] In addition, we found that Sicca syndrome was associated with an increased risk of small intestine and mouth cancers and Guillain-Barré syndrome with soft tissue cancer. Regarding the mechanisms of these findings, overactivation of interleukin (IL)-12 and IL-23 signaling in immune-mediated diseases drives aberrant T_H1 and T_H17 immune responses, leading to chronic inflammation.[4] The IL-23/T_H17/IL-17 axis may reduce barrier function in the skin and local mucosa of the gut and lung and suppress cytotoxic T-cell–mediated antitumor immune surveillance in the involved organs.[23-25] Immunopathology-mediated cell and organ damage, such as that induced by T_H17 activation in inflammation, may also explain our observed associations.[26,27]

Of interest, we found that autoimmune hepatitis, Crohn disease, and ulcerative colitis were associated with increased risk of cancers in the near or distant organs within the gastrointestinal system. This finding could explain why inflammatory bowel disease and ulcerative colitis were associated with extracolorectal cancer risk in our study. Previous studies[9,17,28] have found an association of Crohn disease and ulcerative colitis with hepatobiliary cancer. Despite the increasing evidence for the gut-liver axis[29,30] and gut-oral axis,[31-33] the ob-

Figure 3. Association Profiles of Individual Immune-Mediated Diseases With Risk of Individual Cancers



Red represents a hazard ratio greater than 1; green, hazard ratio less than 1.

[a] $P = .002$ to $P < .05$.

[b] $P < .002$.

served associations of autoimmune hepatitis with tongue and esophageal cancers and ulcerative colitis with tongue cancer have not been reported elsewhere to our knowledge. We also observed an association between immune-mediated disease and risk of cancers in the different systems, such as ulcerative colitis with increased risk of prostate cancer and bullous disorders with laryngeal cancer. Consistent with our findings, 2 nationwide studies in Korea[34] and Denmark[35] reported an increased risk of prostate cancer in patients with ulcerative colitis but not Crohn disease. The association of aberrant fecal microbiome with ulcerative colitis[36] and risk of prostate cancer[37] as well as the anatomical proximity may explain the association. Although case series have reported that patients with mucous membrane pemphigoid may be susceptible to laryngeal cancer,[38] the association of bullous disorders with laryngeal cancer risk has not been reported to our knowledge. Other positive associations of immune-mediated disease with cancers in the different systems, such as idiopathic thrombocytopenic purpura with liver cancer, Graves disease or autoimmune thyroiditis with soft tissue cancer, and psoriasis with lung and laryngeal cancer, have not been reported and need further research. The potential mechanisms include shared triggers such as hepatitis virus,[39] herpesvirus,[40,41] and skin, lung, and oral dysbiosis.[42-44]

In our study, lymphoma was among the cancers most extensively associated with immune-mediated diseases, such as idiopathic thrombocytopenic purpura, systemic lupus erythematosus, rheumatoid arthritis, and allergic rhinitis. Some of these findings have been reported in prior studies.[45-49] The mechanisms may involve chronic antigenic stimulation, inflammation, and shared genetic susceptibility. Of note, compared with solid tumors, lymphoma shares more common genetic components with immune-mediated diseases.[50]

Rheumatoid arthritis, as a systemic disease, had a bidirectional association in our study, with a positive association with lung cancer and lymphoma and a negative association with prostate cancer and breast cancer. These findings are in line with previous reports.[10,11,51] Patients with rheumatoid arthritis manifest oral and lung dysbiosis and pulmonary involvement, which could increase the risk of lung cancer.[52,53] Previous studies[11,54-56] suggest that the inverse associations with prostate and breast cancers are unlikely caused by the use of

anti-inflammatory drugs, consistent with our sensitivity findings. We also found a bidirectional association of type 1 diabetes with cancer risks. Similar observations have been reported previously.[57] The mechanisms for the bidirectional associations of type 1 diabetes and inverse associations of rheumatoid arthritis with risk of certain cancers remain unclear. Although increasing data indicate the diverse role of some immune components (eg, Tregs) and the gut microbiome in the development of different types of cancers,[58,59] more studies are needed to characterize these immune and microbial changes in patients with immune-mediated diseases and elucidate the potential association of these changes with cancer risk.

Strengths and Limitations

The major strengths of this study include the prospective cohort design, large sample size, and comprehensive organ-specific assessment. In addition, we adjusted for a variety of lifestyle risk factors that may have confounded the association of immune-mediated disease and cancer risk.

This study also has some limitations. First, the medications for treatment of immune-mediated diseases were self-reported by participants at recruitment only. No detailed data on dose or duration information were collected, thus precluding a detailed analysis of these medications. However, in line with our sensitivity analysis results, medications for immune-mediated diseases have not been associated with cancer risk[34,46,60-62] and thus are unlikely to have had a substantial confounding effect on our results. Second, the number of cancer cases was small for some rare immune-mediated diseases. Third, despite our use of Bonferroni correction for multiple testing, chance findings could not be ruled out. Fourth, the ascertainment of immune-mediated diseases was based on inpatient records only. We may have missed some diagnoses made in the outpatient setting. However, our reported prevalence of immune-mediated disease appeared to be consistent with those in other studies in Western countries.[2,3] In addition, given the prospective design, any misclassification in the exposure status is likely to have biased the associations toward the null. Fifth, the cohort was relatively young, with a limited number of cases of rare cancers, thus reducing the power to identify associations, particularly for metastatic cancers. Sixth, the cohort participants are predominantly White, and the findings may not be generalizable to other racial and ethnic groups.

Conclusions

In this cohort study, overall immune-mediated diseases were associated with an increased risk of total cancer. Organ-specific immune-mediated diseases had stronger associations with risk of local cancer than extralocal cancer. Many immune-mediated diseases were associated with increased risk of cancers in the involved organs and in the near and distant organs or different systems. These findings support the importance of local and systemic immunoregulation in carcinogenesis and may inform future research elucidating the role of immunoregulation and microbiota in cancer development.

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REFERENCES

1. Palucka AK, Coussens LM. The basis of oncoimmunology. *Cell*. 2016;164(6):1233-1247. doi:10.1016/j.cell.2016.01.049

2. El-Gabalawy H, Guenther LC, Bernstein CN. Epidemiology of immune-mediated inflammatory diseases: incidence, prevalence, natural history, and comorbidities. *J Rheumatol Suppl*. 2010;85(37):2-10. doi:10.3899/jrheum.091461

3. Agrawal M, Shah S, Patel A, Pinotti R, Colombel JF, Burisch J. Changing epidemiology of immune-mediated inflammatory diseases in immigrants: a systematic review of population-based studies. *J Autoimmun*. 2019;105:102303. doi:10.1016/j.jaut.2019.07.002

4. Chyuan IT, Lai JH. New insights into the IL-12 and IL-23: from a molecular basis to clinical application in immune-mediated inflammation and cancers. *Biochem Pharmacol*. 2020;175:113928. doi:10.1016/j.bcp.2020.113928

5. Chunxi L, Haiyue L, Yanxia L, Jianbing P, Jin S. The gut microbiota and respiratory diseases: new

evidence. *J Immunol Res*. 2020;2020:2340670. doi:10.1155/2020/2340670

6. Olén O, Erichsen R, Sachs MC, et al. Colorectal cancer in ulcerative colitis: a Scandinavian population-based cohort study. *Lancet*. 2020;395 (10218):123-131. doi:10.1016/S0140-6736(19)32545-0

7. McGee EE, Castro FA, Engels EA, et al. Associations between autoimmune conditions and hepatobiliary cancer risk among elderly US adults. *Int J Cancer*. 2019;144(4):707-717. doi:10.1002/ijc.31835

8. Emilsson L, Semrad C, Lebwohl B, Green PHR, Ludvigsson JF. Risk of small bowel adenocarcinoma, adenomas, and carcinoids in a nationwide cohort of individuals with celiac disease. *Gastroenterology*. 2020;159(5):1686-1694.e2. doi:10.1053/j.gastro.2020.07.007

9. Mark-Christensen A, Erichsen R, Veres K, Laurberg S, Sørensen HT. Extracolonic cancer risk after total colectomy for inflammatory bowel disease: a population-based cohort study. *J Crohns Colitis*. 2020;14(5):630-635. doi:10.1093/ecco-jcc/jjz199

10. Simon TA, Thompson A, Gandhi KK, Hochberg MC, Suissa S. Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. *Arthritis Res Ther*. 2015;17(1):212. doi:10.1186/s13075-015-0728-9

11. Mercer LK, Davies R, Galloway JB, et al; British Society for Rheumatology Biologics Register (BSRBR) Control Centre Consortium. Risk of cancer in patients receiving non-biologic disease-modifying therapy for rheumatoid arthritis compared with the UK general population. *Rheumatology (Oxford)*. 2013;52(1):91-98. doi:10.1093/rheumatology/kes350

12. Kho ZY, Lal SK. The human gut microbiome—a potential controller of wellness and disease. *Front Microbiol*. 2018;9:1835. doi:10.3389/fmicb.2018.01835

13. Dahan S, Segal Y, Shoenfeld Y. Dietary factors in rheumatic autoimmune diseases: a recipe for therapy? *Nat Rev Rheumatol*. 2017;13(6):348-358. doi:10.1038/nrrheum.2017.42

14. UK Biobank. Protocol for a large-scale prospective epidemiological resources. 2010. Accessed June 1, 2020. https://www.ukbiobank.ac.uk/wp-content/uploads/2011/11/UK-Biobank-Protocol.pdf

15. Wang M, Spiegelman D, Kuchiba A, et al. Statistical methods for studying disease subtype heterogeneity. *Stat Med*. 2016;35(5):782-800. doi:10.1002/sim.6793

16. Liu X, Hemminki K, Försti A, Sundquist J, Sundquist K, Ji J. Cancer risk and mortality in asthma patients: a Swedish national cohort study. *Acta Oncol*. 2015;54(8):1120-1127. doi:10.3109/0284186X.2014.1001497

17. Karlén P, Löfberg R, Broström O, Leijonmarck CE, Hellers G, Persson PG. Increased risk of cancer in ulcerative colitis: a population-based cohort study. *Am J Gastroenterol*. 1999;94(4):1047-1052. doi:10.1111/j.1572-0241.1999.01012.x

18. Card TR, Solaymani-Dodaran M, West J. Incidence and mortality of primary sclerosing cholangitis in the UK: a population-based cohort study. *J Hepatol*. 2008;48(6):939-944. doi:10.1016/j.jhep.2008.02.017

19. Rosenberger A, Bickeböller H, McCormack V, et al. Asthma and lung cancer risk: a systematic investigation by the International Lung Cancer Consortium. *Carcinogenesis*. 2012;33(3):587-597. doi:10.1093/carcin/bgr307

20. Ngu JH, Gearry RB, Frampton CM, Stedman CA. Mortality and the risk of malignancy in autoimmune liver diseases: a population-based study in Canterbury, New Zealand. *Hepatology*. 2012;55(2):522-529. doi:10.1002/hep.24743

21. Elbæk MV, Sørensen AL, Hasselbalch HC. Chronic inflammation and autoimmunity as risk factors for the development of chronic myelomonocytic leukemia? *Leuk Lymphoma*. 2016;57(8):1793-1799. doi:10.3109/10428194.2016.1143938

22. Laniosz V, Torgerson RR, Ramos-Rodriguez AJ, et al. Incidence of squamous cell carcinoma in oral lichen planus: a 25-year population-based study. *Int J Dermatol*. 2019;58(3):296-301. doi:10.1111/ijd.14215

23. Grivennikov SI, Wang K, Mucida D, et al. Adenoma-linked barrier defects and microbial products drive IL-23/IL-17-mediated tumour growth. *Nature*. 2012;491(7423):254-258. doi:10.1038/nature11465

24. Wu S, Rhee KJ, Albesiano E, et al. A human colonic commensal promotes colon tumorigenesis via activation of T helper type 17 T cell responses. *Nat Med*. 2009;15(9):1016-1022. doi:10.1038/nm.2015

25. Calcinotto A, Spataro C, Zagato E, et al. IL-23 secreted by myeloid cells drives castration-resistant prostate cancer. *Nature*. 2018;559(7714):363-369. doi:10.1038/s41586-018-0266-0

26. Manfredo Vieira S, Hiltensperger M, Kumar V, et al. Translocation of a gut pathobiont drives autoimmunity in mice and humans. *Science*. 2018;359(6380):1156-1161. doi:10.1126/science.aar7201

27. Nakamoto N, Sasaki N, Aoki R, et al. Gut pathobionts underlie intestinal barrier dysfunction and liver T helper 17 cell immune response in primary sclerosing cholangitis. *Nat Microbiol*. 2019;4(3):492-503. doi:10.1038/s41564-018-0333-1

28. Mark-Christensen A, Erichsen R, Brandsborg S, et al. Long-term risk of cancer following ileal pouch-anal anastomosis for ulcerative colitis. *J Crohns Colitis*. 2018;12(1):57-62. doi:10.1093/ecco-jcc/jjx112

29. Zhang Q, Ma C, Duan Y, et al. Gut microbiome directs hepatocytes to recruit MDSC and promote cholangiocarcinoma. *Cancer Discov*. 2021;11(5):1248-1267. doi:10.1158/2159-8290.CD-20-0304

30. Wei Y, Li Y, Yan L, et al. Alterations of gut microbiome in autoimmune hepatitis. *Gut*. 2020;69(3):569-577. doi:10.1136/gutjnl-2018-317836

31. Iwauchi M, Horigome A, Ishikawa K, et al. Relationship between oral and gut microbiota in elderly people. *Immun Inflamm Dis*. 2019;7(3):229-236. doi:10.1002/iid3.266

32. Abe K, Fujita M, Hayashi M, Okai K, Takahashi A, Ohira H. Gut and oral microbiota in autoimmune liver disease. *Fukushima J Med Sci*. 2020;65(3):71-75. doi:10.5387/fms.2019-21

33. Peters BA, Wu J, Pei Z, et al. Oral microbiome composition reflects prospective risk for esophageal cancers. *Cancer Res*. 2017;77(23):6777-6787. doi:10.1158/0008-5472.CAN-17-1296

34. Jung YS, Han M, Park S, Kim WH, Cheon JH. Cancer risk in the early stages of inflammatory bowel disease in Korean patients: a nationwide population-based study. *J Crohns Colitis*. 2017;11(8):954-962. doi:10.1093/ecco-jcc/jjx040

35. Kappelman MD, Farkas DK, Long MD, et al. Risk of cancer in patients with inflammatory bowel diseases: a nationwide population-based cohort study with 30 years of follow-up evaluation. *Clin Gastroenterol Hepatol*. 2014;12(2):265-73.e1. doi:10.1016/j.cgh.2013.03.034

36. Schirmer M, Franzosa EA, Lloyd-Price J, et al. Dynamics of metatranscription in the inflammatory bowel disease gut microbiome. *Nat Microbiol*. 2018;3(3):337-346. doi:10.1038/s41564-017-0089-z

37. Liss MA, White JR, Goros M, et al. Metabolic biosynthesis pathways identified from fecal microbiome associated with prostate cancer. *Eur Urol*. 2018;74(5):575-582. doi:10.1016/j.eururo.2018.06.033

38. La Placa M, Balestri R, Tartari F, et al. Mucous membrane pemphigoid-associated malignancies: case series and a brief overview of the literature. *Dermatol Pract Concept*. 2019;9(2):119-125. doi:10.5826/dpc.0902a07

39. Johira Y, Hatooka H, Mori N, et al. Regression of idiopathic thrombocytopenic purpura in a patient with eradication of hepatitis C virus by direct-acting antivirals. *Hepatology*. 2020;71(1):389-391. doi:10.1002/hep.30900

40. Sultanova A, Cistjakovs M, Gravelsina S, et al. Association of active human herpesvirus-6 (HHV-6) infection with autoimmune thyroid gland diseases. *Clin Microbiol Infect*. 2017;23(1):50, e51-e55.

41. Mesri EA, Cesarman E, Boshoff C. Kaposi's sarcoma and its associated herpesvirus. *Nat Rev Cancer*. 2010;10(10):707-719. doi:10.1038/nrc2888

42. Fahlén A, Engstrand L, Baker BS, Powles A, Fry L. Comparison of bacterial microbiota in skin biopsies from normal and psoriatic skin. *Arch Dermatol Res*. 2012;304(1):15-22. doi:10.1007/s00403-011-1189-x

43. Liu HX, Tao LL, Zhang J, et al. Difference of lower airway microbiome in bilateral protected specimen brush between lung cancer patients with unilateral lobar masses and control subjects. *Int J Cancer*. 2018;142(4):769-778. doi:10.1002/ijc.31098

44. Hayes RB, Ahn J, Fan X, et al. Association of oral microbiome with risk for incident head and neck squamous cell cancer. *JAMA Oncol*. 2018;4(3):358-365. doi:10.1001/jamaoncol.2017.4777

45. Elfström P, Granath F, Ekström Smedby K, et al. Risk of lymphoproliferative malignancy in relation to small intestinal histopathology among patients with celiac disease. *J Natl Cancer Inst*. 2011;103(5):436-444. doi:10.1093/jnci/djq564

46. Hellgren K, Baecklund E, Backlin C, Sundstrom C, Smedby KE, Askling J. Rheumatoid arthritis and risk of malignant lymphoma: is the risk still increased? *Arthritis Rheumatol*. 2017;69(4):700-708. doi:10.1002/art.40017

47. Klein A, Polliack A, Gafter-Gvili A. Systemic lupus erythematosus and lymphoma: incidence, pathogenesis and biology. *Leuk Res*. 2018;75:45-49. doi:10.1016/j.leukres.2018.11.004

48. Rafiq M, Hayward A, Warren-Gash C, et al. Allergic disease, corticosteroid use, and risk of Hodgkin lymphoma: a United Kingdom nationwide

case-control study. *J Allergy Clin Immunol*. 2020;145(3):868-876. doi:10.1016/j.jaci.2019.10.033

49. Fallah M, Liu X, Ji J, Försti A, Sundquist K, Hemminki K. Autoimmune diseases associated with non-Hodgkin lymphoma: a nationwide cohort study. *Ann Oncol*. 2014;25(10):2025-2030. doi:10.1093/annonc/mdu365

50. Din L, Sheikh M, Kosaraju N, et al. Genetic overlap between autoimmune diseases and non-Hodgkin lymphoma subtypes. *Genet Epidemiol*. 2019;43(7):844-863. doi:10.1002/gepi.22242

51. Huang WK, Chiou MJ, Kuo CF, Lin YC, Yu KH, See LC. No overall increased risk of cancer in patients with rheumatoid arthritis: a nationwide dynamic cohort study in Taiwan. *Rheumatol Int*. 2014;34(10):1379-1386. doi:10.1007/s00296-014-2982-6

52. Lopez-Oliva I, Paropkari AD, Saraswat S, et al. Dysbiotic subgingival microbial communities in periodontally healthy patients with rheumatoid arthritis. *Arthritis Rheumatol*. 2018;70(7):1008-1013. doi:10.1002/art.40485

53. Scher JU, Joshua V, Artacho A, et al. The lung microbiota in early rheumatoid arthritis and autoimmunity. *Microbiome*. 2016;4(1):60. doi:10.1186/s40168-016-0206-x

54. Brasky TM, Velicer CM, Kristal AR, Peters U, Potter JD, White E. Nonsteroidal anti-inflammatory drugs and prostate cancer risk in the VITamins And Lifestyle (VITAL) cohort. *Cancer Epidemiol Biomarkers Prev*. 2010;19(12):3185-3188. doi:10.1158/1055-9965.EPI-10-0942

55. Wadström H, Pettersson A, Smedby KE, Askling J. Risk of breast cancer before and after rheumatoid arthritis, and the impact of hormonal factors. *Ann Rheum Dis*. 2020;79(5):581-586. doi:10.1136/annrheumdis-2019-216756

56. Cairat M, Al Rahmoun M, Gunter MJ, Severi G, Dossus L, Fournier A. Use of nonsteroidal anti-inflammatory drugs and breast cancer risk in a prospective cohort of postmenopausal women. *Breast Cancer Res*. 2020;22(1):118. doi:10.1186/s13058-020-01343-1

57. Harding JL, Shaw JE, Peeters A, Cartensen B, Magliano DJ. Cancer risk among people with type 1 and type 2 diabetes: disentangling true associations, detection bias, and reverse causation. *Diabetes Care*. 2015;38(2):264-270. doi:10.2337/dc14-1996

58. Wing JB, Tanaka A, Sakaguchi S. Human FOXP3^{+} regulatory T cell heterogeneity and function in autoimmunity and cancer. *Immunity*. 2019;50(2):302-316. doi:10.1016/j.immuni.2019.01.020

59. Helmink BA, Khan MAW, Hermann A, Gopalakrishnan V, Wargo JA. The microbiome, cancer, and cancer therapy. *Nat Med*. 2019;25(3):377-388. doi:10.1038/s41591-019-0377-7

60. Sepriano A, Kerschbaumer A, Smolen JS, et al. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2019 update of the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis*. 2020;79(6):760-770. doi:10.1136/annrheumdis-2019-216653

61. Lopez-Olivo MA, Tayar JH, Martinez-Lopez JA, et al. Risk of malignancies in patients with rheumatoid arthritis treated with biologic therapy: a meta-analysis. *JAMA*. 2012;308(9):898-908. doi:10.1001/2012.jama.10857

62. Chen Y, Friedman M, Liu G, Deodhar A, Chu CQ. Do tumor necrosis factor inhibitors increase cancer risk in patients with chronic immune-mediated inflammatory disorders? *Cytokine*. 2018;101:78-88. doi:10.1016/j.cyto.2016.09.013