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Research article

Association between autoimmunity-related disorders and prostate cancer: A Mendelian randomization study☆

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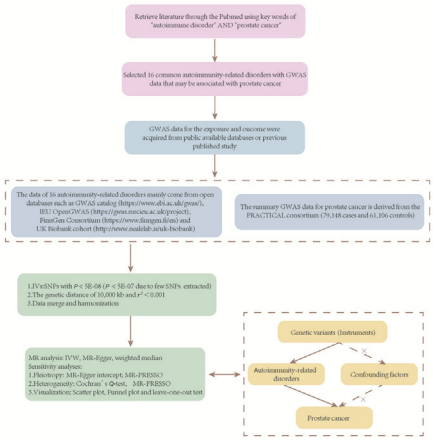
HIGHLIGHTS

- The association between autoimmunity-related disorders and prostate cancer was explored using Mendelian randomization (MR).
- MR is an epidemiological analysis method used to verify etiological hypotheses using genome-wide association study (GWAS) data.
- The results suggested a correlation between six diseases and prostate cancer. Further research is needed to explore the underlying mechanisms of comorbidities at the molecular level.

GRAPHICAL ABSTRACT



Workflow of MR study. (A) We retrieved literature from PubMed to explore the relationship between autoimmune disorders and prostate cancer. (B) We selected and extracted GWAS data of 16 common autoimmunity-related disorders that may be associated with prostate cancer. (C) We explored the potential relationship between the selected autoimmune disorders and prostate cancer through MR analysis. (D) MR analysis selected genetic variants as instrumental variants which are strongly correlated with exposure factors and cannot be associated with any other possible confounding factors. GWAS: genome-wide association study; IEU: Integrative Epidemiology Unit; IVs: Instrumental variants; IVW: Inverse variance weighting; MR: Mendelian randomization; PRACTICAL: Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome; PRESSO: Pleiotropy residual sum and outlier; SNPs: Single-nucleotide polymorphisms.

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ABSTRACT

Background: Although many epidemiological studies and meta-analyses have reported an association between autoimmune disorders and prostate cancer, none has reported a clear correlation or the direction of the association. The purpose of our study was to explore the potential relationship between autoimmunity-related disorders and prostate cancer using Mendelian randomization (MR).

Methods: We retrieved literature from PubMed using the keywords "autoimmune disorder" AND "prostate cancer" to find more clues on the correlation between prostate cancer and autoimmunity-related disorder. Based on this literature search, we selected 16 autoimmunity-related disorders that had genome-wide association study (GWAS)

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data and may be associated with prostate cancer. The inverse variance weighting (IVW) method was applied as our primary analysis for two-sample MR and multivariate MR analysis to estimate the odds ratio (OR) and 95% confidence interval (CI). We further verified the robustness of our conclusions using a series of sensitivity analyses.
Results: The autoimmunity-related diseases selected include rheumatoid arthritis, ankylosing spondylitis, coxarthrosis, gonarthrosis, Crohn's disease, ulcerative colitis, irritable bowel syndrome, celiac disease, primary sclerosing cholangitis, asthma, type 1 diabetes, systemic lupus erythematosus, multiple sclerosis, autoimmune hyperthyroidism, psoriatic arthropathies, and polymyalgia rheumatica. The results of inverse variance weighting (IVW suggested that six diseases were associated with the development of prostate cancer. The three diseases that may increase the risk of prostate cancer are rheumatoid arthritis ($P = 0.001$), coxarthrosis ($P < 0.001$), and gonarthrosis ($P = 0.008$). The three possible protective factors against prostate cancer are primary sclerosing cholangitis ($P = 0.001$), autoimmune hyperthyroidism ($P = 0.011$), and psoriatic arthropathies ($P = 0.001$). Horizontal pleiotropy was not observed in the MR-Egger test.
Conclusions: Our findings provide predictive genetic evidence for an association between autoimmune disorders and prostate cancer. Further research is needed to explore the underlying mechanisms of comorbidities at the molecular level.

Introduction

Autoimmunity-related diseases are diseases in which the body attacks its own tissues owing to immune system dysfunction. When lymphocytes (T and B cells) are influenced by different external and internal factors, they attack various tissues and organs of the body, causing denaturation, damage, and dysfunction. People with autoimmune disorders suffer from chronic inflammation, which can affect almost every organ and system in the body.

Chronic inflammation is a type of systemic inflammation that persists for months or years, and it is associated with almost every disease. Many studies have suggested a close relationship between inflammation and carcinogenesis, and inflammation may precede or accompany tumor development. There are well-established examples of cancers caused by chronic inflammation, including stomach cancer caused by *Helicobacter pylori* infection, cervical cancer caused by human papillomavirus infection, rheumatoid arthritis, and lung cancer. With the introduction of the concept of the immune microenvironment in tumor tissues, there is increasing awareness of the existence of many immune cells in the tumor microenvironment. Immune cells regulate one another through cytokines and play important roles in tumor initiation, progression, invasion, and metastasis.

Worldwide, prostate cancer (PCA) ranks second among male malignant tumors in terms of morbidity. In the United States, the incidence of PCA has surpassed that of lung cancer, making it the most serious malignant tumor endangering men's health.[1,2] Although the morbidity rate of PCA in China is lower than that in Western countries, it has increased substantially in recent years, particularly in the developed coastal areas. Therefore, PCA has become the most common malignant tumor that affects the male reproductive system.

Currently, the mechanism of immune function in tumorigenesis is one of the main areas of research. Many studies support a close association between autoimmune disorders and tumors, based on two hypotheses. On one hand, autoimmune disorders originate from over-activation of the immune system, leading to enhanced immune surveillance and recognition, which helps to identify and eliminate cancer cells. In contrast, some researchers believe that an over-activated immune system triggers chronic inflammation, leading to carcinogenic DNA mutations in dividing cells. Association of autoimmune disorders with increased risk of PCA may indicate a common genetic structure between these diseases. One study also found that the use of androgen deprivation therapy in patients with PCA was associated with a reduced risk of autoimmunity-related disorders. This provides further evidence of a potential link between the two.[3] However, few studies have been conducted in this regard.

Mendelian randomization (MR) is an epidemiological analysis method used to verify etiological hypotheses and inferences.[4] Specifically, it uses genetic variation as an instrumental variant (IV) to infer the correlation between exposure and outcome. Exposure refers to the research object being subjected to a certain substance, state, or characteristic. In epidemiology, an outcome is defined as a consequence of exposure and usually refers to a disease. In previous epidemiological studies, we regularly encountered confounding factors leading to inaccurate associations. Simultaneously, many risks cannot be assigned randomly, for ethical reasons. Finally, reverse causation may be found when studying the associations between diseases. In traditional research, the causal relationship between exposure and outcomes can only be studied using randomized controlled trials (RCTs). However, RCTs require time, effort, and money, and are also limited by ethical factors. Mendelian randomized analysis selects genetic variants from random allocation of parental alleles, which is similar to RCTs in principle. Therefore, it can compensate for the above shortcomings of epidemiological studies and RCTs. It uses IVs to replace exposure factors that cannot be experimentally studied. By measuring the correlation among genetic variation, exposure, and outcome, MR can infer an approximate causal relationship between exposure and outcome.[5,6]

For the results of MR to be reliable, three basic assumptions must be satisfied, as follows. (1) Correlation: instrumental variables are strongly correlated with exposure factors ($P < 5E{-}08$); (2) independence: instrumental variables cannot be associated with any other possible confounding factors; and (3) exclusivity: instrumental variables are not directly related to the outcome factors.

This study aimed to clarify the relationship between autoimmunity-related diseases and PCA by conducting MR analysis on genome-wide association study (GWAS) data.

Methods

Study samples and measures

We retrieved literature from PubMed, using the keywords “autoimmune disorder” AND “cancer” and found that >10 autoimmune disorders are potentially related to cancer. We proceeded to use the keywords “autoimmune disorder” AND “prostate cancer” to find more clues on the correlation between PCA and autoimmune diseases. Based on this literature search, we selected 16 common autoimmunity-related disorders that had GWAS data and may be associated with PCA, and we explored the potential relationship between them and PCA through MR analysis. During the review of previous publications, we identified one study that reported an association between ankylosing spondylitis and PCA, and suggested a correlation between elderly osteoarthritis (including gonarthrosis and coxarthrosis) and PCA. Although gonarthrosis and coxarthrosis are not traditionally classified as autoimmune disorders, they are closely associated with advanced age and chronic inflammation. In addition, our research identified a correlation between rheumatoid arthritis, psoriatic arthropathies, and PCA. Considering the close association of the progression of elderly osteoarthritis with immune cells and cytokines, we further investigated the association between these two autoimmunity-related disorders and PCA.

We used the largest public GWAS dataset available for computation to determine the association between autoimmune diseases and PCA. Data on autoimmune diseases were obtained from open databases, such as the GWAS catalog (https://www.ebi.ac.uk/gwas/), Integrative Epidemiology Unit (IEU) OpenGWAS (https://gwas.mrcieu.ac.uk), FinnGen Consortium (https://www.finngen.fi/en), and the UK Biobank cohort (http://www.nealelab.is/uk-biobank)[7–17] [Table 1]. Each dataset includes specific information but is not limited to screening procedures and diagnostic criteria, which are recorded in open databases or original published literature. The data samples used for analysis were of European ancestry, and there was no significant overlap among them.

Summary GWAS data for PCA were derived from the Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome (PRACTICAL) Consortium. This study included 79,148 cases of PCA and 61,106 controls. We included 20,346,368 single-nucleotide polymorphisms (SNPs). The summary data are the results of a meta-analysis originating from seven previous PCA GWAS and current genotypic data using a custom array, namely the OncoArray. Most of the studies were case–control studies. The dataset contains the patients' clinical information, including, but not limited to, age at diagnosis, family history of cancer, and clinical factors (such as Gleason score and prostate-specific antigen [PSA]).

Instrument selection

To select genetic variation from the GWAS data of 16 autoimmunity-related disorders, we used a subset function to extract SNPs significantly associated with exposure in the GWAS ($P < 5E{-}08$); $P < 5E{-}07$ was used as the significance threshold to screen cases of multiple sclerosis (MS) and rheumatic myalgia due to the small number of SNPs extracted. The LDproxyR tool of the TwoSampleMR package was used to remove possible imbalance effects between SNPs (clumping window of 10,000 kb, clumping cutoff r^2 of 0.001). This tool can also remove variants containing palindromic sequences. Subsequently, the SNPs filtered from autoimmunity-related diseases were merged with the GWAS data of PCA, and the SNPs selected in this study were confirmed through a harmonization step. If the results were heterogeneous, outliers were eliminated by MR pleiotropy residual sum and outlier (MR-PRESSO), and the effect value was re-evaluated. In addition, we calculated and excluded IVs with *F*-test values < 10 to avoid situations where instrumental variables are not strongly correlated with exposure factors, or where instrumental variables explain only a small part of the phenotypic variation [Supplementary data 1]. Finally, we searched http://www.phenoscanner.medschl.cam.ac.uk/to identify all diseases associated with the selected variants. If one IV was associated with risk factors that may lead to the disease, it was eliminated to avoid confounding factors.

Table 1
Characteristics of the prostate cancer and autoimmunity-related disease GWAS cohorts.

Exposure	Number of cases	Number of controls	Number of SNPs	PMID/ consortium
Asthma	56,167	352,255	34,551,291	34103634
Celiac disease	12,041	12,228	38,037	22057235
Primary sclerosing cholangitis	2871	12,019	7,891,603	27992413
Type 1 diabetes	9266	15,574	12,783,129	32005708
Systemic lupus erythematosus	5201	9066	7,071,163	26502338
Rheumatoid arthritis	14,361	43,923	13,108,512	33310728
Ankylosing spondylitis	9069	13,578	99,962	23749187
Coxarthrosis	10,709	172,834	16,380,348	FinnGen biobank
Ulcerative colitis	12,366	33,609	9,474,559	28067908
Crohn's disease	12,194	28,072	9,457,998	28067908
Multiple sclerosis	47,429	68,374	6,304,359	31604244
Irritable bowel syndrome	53,400	430,957	9,885,498	34741163
Autoimmune hyperthyroidism	962	172,976	16,380,189	FinnGen biobank
Psoriatic arthropathies	1553	147,221	16,380,141	FinnGen biobank
Polymyalgia rheumatic	1523	213,145	16,380,452	FinnGen biobank
Gonarthrosis	22,796	172,834	16,380,379	FinnGen biobank
Prostate cancer	79,148	61,106	20,346,368	29892016

GWAS: Genome-wide association study; PMID: PubMed identification number; SNPs: Single-nucleotide polymorphisms.

Study design

Our data analysis had three main aspects. First, the association between autoimmunity-related disorders and PCA was investigated using a two-sample MR method. Secondly, as Crohn's disease (CD) and ulcerative colitis (UC) overlap in a significant number of SNPs, we used multivariate MR analyses to distinguish their direct associations with PCA. Finally, we conducted a series of sensitivity analyses to evaluate the reliability of the results, eliminate possible confounding factors, and improve the accuracy of the conclusions.

Statistical analysis

We conducted a two-sample MR study using the TwoSampleMR package. We calculated the Wald ratio of each SNP and meta-analyzed the effect value of each SNP using inverse variance weighting (IVW) and two other methods to generate a conclusive β estimate. The odds ratio (OR) and 95% confidence interval (CI) were converted as analysis results. The relationship between exposure and outcome was evaluated based on a type I error of 0.05. The IVW method is sensitive to pleiotropy and provides the most reliable estimates of causality.[18] In addition to IVW, two other methods in the Mendelian analysis, namely MR-Egger and weighted median, were used as supplementary analyses to further verify the stability of the IVW results. The tolerance of the weighted median for genetic tools is high, and the assessment of causality is reliable when >50% of the SNPs are effective.[19] MR-Egger can also correct for pleiotropy in causal assessment.[20] Additionally, we tested the heterogeneity of the conclusions using Cochran's *Q*-test for the MR-Egger and IVW methods. Heterogeneity existed when $P < 0.05$. We further identified and eliminated SNPs that may produce heterogeneity through MR-PRESSO analysis and re-performed the MR analysis after eliminating outliers.[21] To verify the second and third hypotheses, we used MR-Egger to determine the existence of horizontal pleiotropy.[22] In addition, we provided scatter plots to visualize the relationship between exposure and outcomes. Finally, to verify the reliability of the positive results, we carried out a leave-one-out analysis and drew a funnel diagram. All data analyses were performed using the R software (version 4.2.1). We used TwoSampleMR (https://github.com/MRCIEU/TwoSampleMR) and multivariate (MV)MR for MR analysis.[23,24]

Results

Mendelian randomization analysis

Among the 16 autoimmunity-related disorders, IVW results suggested that six genetically predicted autoimmune diseases were significantly associated with the risk of PCA [Table 2]. The three diseases that may increase the risk of PCA are rheumatoid arthritis (OR: 1.026, 95% CI: 1.009–1.043, $P = 0.001$), coxarthrosis (OR: 1.165, 95% CI: 1.079–1.258, $P < 0.001$), and gonarthrosis (OR: 1.166, 95% CI: 1.040–1.308, $P = 0.008$). The three possible protective factors against PCA are primary sclerosing cholangitis (PSC) (OR: 0.971, 95% CI: 0.955–0.988, $P = 0.001$), autoimmune hyperthyroidism (OR: 0.965, 95% CI: 0.939–0.992, $P = 0.011$), and psoriatic arthropathies (OR: 0.972, 95% CI:

Table 2
Estimates of the association between autoimmune disease exposure and prostate cancer, computed by two-sample MR analysis.

Exposure	Number of SNP	IVW			Weighted median			MR-Egger		
		OR	CI	*P*	OR	CI	*P*	OR	CI	*P*
Asthma	70	1.044	0.999–1.091	0.055	1.065	1.008–1.126	0.024	1.079	0.965–1.206	0.189
Celiac disease	15	0.989	0.969–1.010	0.304	0.992	0.974–1.010	0.371	1.003	0.974–1.032	0.851
Primary sclerosing cholangitis	18	0.971	0.955–0.988	0.001	0.971	0.955–0.988	0.001	0.967	0.944–0.992	0.019
Type 1 diabetes	39	1.006	0.989–1.025	0.445	1.018	0.995–1.042	0.118	1.021	0.981–1.061	0.321
Systemic lupus erythematosus	40	0.996	0.984–1.008	0.516	1.001	0.985–1.017	0.931	0.992	0.965–1.019	0.560
Rheumatoid arthritis	84	1.026	1.009–1.043	0.002	1.024	1.001–1.048	0.041	1.039	1.014–1.065	0.003
Ankylosing spondylitis	24	1.061	0.963–1.169	0.229	1.099	1.001–1.207	0.047	1.089	0.925–1.284	0.316
Coxarthrosis	6	1.165	1.079–1.258	< 0.001	1.142	1.041–1.252	< 0.001	0.933	0.588–1.479	< 0.001
Ulcerative colitis	51	0.989	0.968–1.010	0.318	0.973	0.946–1.001	0.061	0.936	0.884–0.993	0.033
Crohn's disease	79	0.987	0.974–1.002	0.085	0.991	0.971–1.011	0.381	1.001	0.964–1.038	0.975
Multiple sclerosis	85	1.007	0.993–1.021	0.360	1.007	0.985–1.030	0.513	1.016	0.996–1.037	0.118
Irritable bowel syndrome	5	0.953	0.781–1.162	0.632	0.918	0.716–1.176	0.499	0.157	0.016–1.530	0.209
Autoimmune hyperthyroidism	6	0.965	0.939–0.992	0.011	0.958	0.935–0.982	0.001	0.938	0.876–1.004	0.138
Psoriatic arthropathies	4	0.972	0.955–0.989	0.001	0.969	0.950–0.989	0.002	0.953	0.905–1.003	0.206
Polymyalgia rheumatic	5	1.017	0.977–1.058	0.404	1.028	1.001–1.056	0.037	1.034	0.935–1.144	0.557
Gonarthrosis	5	1.166	1.040–1.308	0.008	1.09	0.957–1.243	0.194	2.118	0.933–4.805	0.170

CI: Confidence interval; IVW: Inverse variance weighting; MR: Mendelian randomization; OR: Odds ratio; SNP: Single-nucleotide polymorphism.

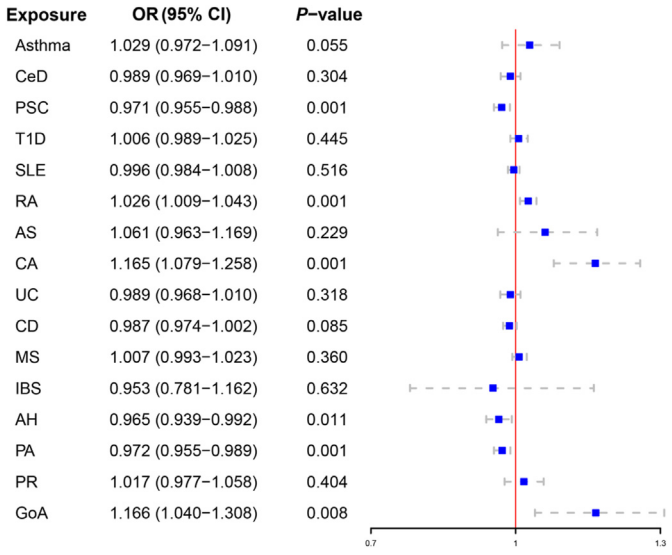

Figure 1. Forest plot to visualize estimates of the association between autoimmunity-related disorders and prostate cancer by IVW. AH: Autoimmune hyperthyroidism; AS: Ankylosing spondylitis; CA: Coxarthrosis; CD: Crohn's disease; CeD: Celiac disease; CI: Confidence interval; GoA: Gonarthrosis; IBS: Irritable bowel syndrome; IVW: Inverse variance weighting; MS: Multiple sclerosis; OR: Odds ratio; PA: Psoriatic arthropathies; PR: Polymyalgia rheumatic; PSC: Primary sclerosing cholangitis; RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus; T1D: Type 1 diabetes; UC: Ulcerative colitis.

0.955–0.989, $P = 0.001$) [Figure 1]. For rheumatoid arthritis, coxarthrosis, and PSC, the weighted median method and MR-Egger test showed similar results in the same direction ($P < 0.05$). The weighted median method showed similar results for gonarthrosis, autoimmune hyperthyroidism, and psoriatic arthritis ($P < 0.05$). Horizontal pleiotropy was not observed in the MR-Egger intercepts. MVMR analysis results were consistent with the previous results, and we did not find an association between CD or UC and PCA [Table 3]. In addition, scatter plots visually demonstrated the association between autoimmunity-related disorders and PCA [Supplementary date 2 A].

Sensitivity analysis

We used two methods to conduct Cochran's *Q*-test to detect heterogeneity among the samples. When the *Q*-*P* value of the heterogeneity test ≤0.05, it indicated heterogeneity in the analysis result. After heterogeneity was found, MR-PRESSO analysis was performed to identify SNPs that may have caused heterogeneity, in which the parameter NbDistribution = 10,000. MR and sensitivity analyses were repeated after the corresponding SNPs were removed [Table 4]. We found 12 cases of outcome heterogeneity. When heterogeneity existed, we used the random effects model of the IVW method to evaluate the effect values. MR-Egger test was used to detect horizontal pleiotropy. In this study, the *P*-values of the analysis results were all >0.05, which did not provide evidence of horizontal pleiotropy.

Table 3
Estimates of the association between ulcerative colitis and Crohn's disease, and prostate cancer, computed by multivariate Mendelian randomization analysis.

Exposure	SNP, *n*	*B*	SE	OR (95% CI)	*P*
Ulcerative colitis	46	0.012	0.014	0.987 (0.959–1.016)	0.394
Crohn's disease	73	−0.003	0.011	0.996 (0.974–1.019)	0.765

CI: Confidence interval; OR: Odds ratio; SE: Standard error; SNP: Single-nucleotide polymorphism.

For the six diseases found to be associated with PCA, the leave-one-out method was used to assess the impact of each SNP on the overall causal estimates; that is, after each exclusion of one SNP, the remaining SNPs were re-analyzed as instrumental variables [Supplementary data 2B]. The results of the reserve method for rheumatoid arthritis, coxarthrosis, gonarthrosis, and PSC showed that after the SNPs were sequentially removed, the results of IVW analysis of the remaining SNPs were similar to those of the analysis that included all SNPs, and no SNP was found to have a significant effect on the estimate of causal association. Autoimmune hyperthyroidism and psoriatic arthropathies each had one SNP that crossed the origin, owing to the small number of SNPs. We also checked the stability of the results by examining the symmetry of funnel plots [Supplementary data 2C].

Discussion

Inflammation plays a double-edged role in the body, protecting it from pathogens and monitoring abnormal cells. However, chronic inflammation can cause tissue damage. Previous studies have identified mechanisms by which inflammation leads to cancer, and stomach, liver, and cervical cancers are thought to be associated with inflammation. In recent years, the relationship between chronic inflammation, autoimmune disorders, and cancer has attracted increasing attention; however, few studies have been conducted in this regard in the field of PCA. In this study, we conducted an MR analysis of 16 autoimmunity-related disorders and PCA to systematically and comprehensively demonstrate their

Table 4
Sensitivity analysis, heterogeneity test, and pleiotropy test to verify MR assumption.

Exposure	Heterogeneity test						Pleiotropy			MR-PRESSO
	MR-Egger			IVW			MR-Egger			Outlier SNP
	Q	*Q*_df	*P*_*P* value	*Q*	*Q*_df	*P*_*P* value	Intercept	SE	*P*	
Irritable bowel syndrome	2.447	3	0.485	4.931	4	0.301	0.076	0.049	0.217	
Autoimmune hyperthyroidism	9.578	4	0.048	11.515	5	0.042	0.016	0.018	0.419	
Coxarthrosis	4.431	4	0.350	5.449	5	0.360	0.025	0.027	0.392	
Asthma	108.355	68	0.001	108.970	69	0.001	−0.002	0.004	0.535	rs10486391, rs2412099, rs7936312, rs9260752, rs9272226
Celiac disease	22.624	11	0.020	26.084	12	0.010	−0.007	0.006	0.221	rs130078, rs13198474
Primary sclerosing cholangitis	37.432	16	0.002	37.913	17	0.003	0.003	0.006	0.656	
Type 1 diabetes	56.924	37	0.019	57.772	38	0.021	−0.004	0.005	0.462	rs9273363, rs689, rs506770, rs4566101
Systemic lupus erythematosus	66.000	39	0.004	69.312	40	0.003	0.007	0.005	0.169	
Rheumatoid arthritis	140.149	82	<0.001	143.300	83	<0.001	−0.003	0.002	0.178	rs112733823, rs11754264, rs1611236
Ankylosing spondylitis	54.411	38	0.041	54.572	39	0.049	0.001	0.005	0.739	rs2517655
Ulcerative colitis	74.431	49	0.011	80.221	50	0.004	0.009	0.005	0.056	rs2212434, rs6062496
Crohn's disease	96.787	77	0.063	97.500	78	0.067	−0.002	0.003	0.453	rs11236797, rs6062496, rs6808936
Multiple sclerosis	138.343	83	<0.01	141.186	84	<0.01	−0.002	0.002	0.195	rs11711621
Psoriatic arthropathies	1.042	2	0.594	1.684	3	0.641	0.012	0.014	0.507	
Polymyalgia rheumatic	10.530	3	0.015	11.007	4	0.026	−0.007	0.019	0.737	
Gonarthrosis	3.113	3	0.374	5.263	4	0.261	−0.049	0.034	0.246	rs1558902, rs224329

IVW: Inverse variance weighting; MR: Mendelian randomization; PRESSO: Pleiotropy residual sum and outlier; *Q*: Cochran's *Q* statistic; *Q*_df: Cochran's *Q* statistic (degree of freedom); SE: Standard error; SNP: Single-nucleotide polymorphism.

correlation. Using MR, we further corroborated previously reported observational findings, laying the foundation for exploring deeper associations at the molecular level. To prove the reliability of the results of this study, we applied a series of analysis methods to ensure that the results meet the three core assumptions of MR analysis and improve the robustness and validity of the results.

Based on MR, we comprehensively explored the association between autoimmunity-related disorders and PCA at the genetic level.

Previous observational studies have reported an association between rheumatic diseases and PCA. Wheeler et al.[25] published a retrospective cohort study in 2022, which was the largest clinical study on rheumatoid arthritis and PCA involving 283,798 patients (>56,000 patients with rheumatoid arthritis) and 6550 patients with PCA (patients with rheumatoid arthritis >1400 cases). They found that rheumatoid arthritis was associated with an increased risk of PCA (adjusted hazard ratio [HR]: 1.14, 95% CI: 1.06–1.22), but cohort bias was inevitable. Through MR analysis, we further supported the hypothesis that arthritis may be a risk factor for PCA. Another study found that higher cytokine/chemokine concentrations in patients with rheumatoid arthritis were associated with increased risk of cancer, particularly lung and lymphoproliferative cancers, suggesting that elevated levels of circulating cytokines and chemokines predicted the risk of cancer in patients with rheumatoid arthritis.[26] Two meta-analyses have shown that systemic lupus erythematosus (SLE) may reduce the incidence of PCA, which is inconsistent with our findings.[27,28] This may be because men with SLE tend to have low levels of androgens, which play an important role in the proliferation of PCA cells. However, it is worth noting that Song et al.[29] found that SLE was positively associated with most cancers, and it was negatively associated with only PCA and cutaneous melanoma. Several co-stimulators have been shown to play important roles in the carcinogenic process associated with SLE. These stimulators may neutralize or reverse the effects of testosterone on PCA. However, due to horizontal pleiotropy, observational studies have not been able to exclude the effect of anti-rheumatic drugs such as non-steroidal anti-inflammatory drugs (NSAIDs).[30] Simultaneously, because SLE is more common in females, observational studies among male patients are relatively insufficient. Similarly to our conclusion, Ward and Alehashemi[31] found that older patients with knee and hip osteoarthritis (KHOA) or ankylosing spondylitis were more likely to develop PCA. Our study found no association between ankylosing spondylitis and PCA after removing SNPs that led to pleiotropy; therefore, confounding factors may have interfered. A large matching clinical study showed that patients with rheumatic myalgia were 6% more likely to develop cancer in the 6 months following diagnosis than those without rheumatic myalgia.[32] There was a slight increase in PCA incidence, but the number of cases was too small for a direct comparison. However, this association weakened over time.[33] Therefore, larger clinical studies are required to support this hypothesis.

Epidemiological studies suggest an association between gastrointestinal autoimmune diseases and PCA. In addition to an increased risk of gastrointestinal malignancies, patients with inflammatory bowel disease (IBD) may also have an increased risk of extra-intestinal tumors.[34] A matched retrospective cohort study showed that IBD was associated with an increased risk of PCA.[35] A meta-analysis further demonstrated that patients with UC had a higher risk of PCA by subgroup analysis, whereas CD was not associated with PCA.[36] Although the cohort study selected 1:9 cases, the number of IBD cases was 1000, which was limited. Recent studies have suggested that the intestinal microenvironment may affect prostate inflammation and the occurrence of PCA.[37,38] The meta-analysis selected both cohort and case–control studies; therefore, we could not infer whether IBD caused PCA or PCA was caused by immunosuppressive drugs used in patients with IBD. More targeted studies are required for further verification. PSC, celiac disease, and irritable bowel syndrome, which are associated with the development of IBD, were also included in this study to explore their associations with PCA. PSC has a low incidence rate and is characterized by multifocal bile duct stenosis and advanced liver disease. No previous study has reported an association between PSC and PCA; however, PSC disrupts male estrogen levels in patients by causing liver failure, and this may prevent the development of PCA.

With respect to autoimmune diseases of the central nervous system, studies on systemic sclerosis and PCA are ambiguous. However, a recently published meta-analysis that pooled the results of all studies on the subject showed no association between systemic sclerosis and PCA.[39] Notably, testosterone levels are significantly reduced in patients with MS, and this may have implications on the development of PCA.[40]

Regarding chronic diseases, Harding et al.[41] found that type 1 diabetes (T1D) was associated with reduced incidence of PCA but not with mortality. In contrast, Kang et al.[42] found that T1D was associated with higher morbidity in PCA with a Gleason score of 8–10, in contrast to PCA

with a Gleason score of 7. Hyperimmune function and hyperglycemia may promote the proliferation of tumor cells. Additionally, exogenous insulin and insulin-like growth factor 1(IGF-1) can promote carcinogenesis.[43,44] However, high insulin levels also lead to a decrease in testosterone levels, which appears to lower the risk of PCA.[45] To resolve these disputes, we selected the largest GWAS dataset of T1D for MR analysis and found no correlation between it and PCA.

Severi et al., [46] who first conducted a cohort study in Melbourne in 2010, found a slightly increased risk of PCA in patients with asthma (HR: 1.25, 95% CI: 1.05–1.49). It is important to note that it is difficult to separate the effects of glucocorticoids from those of asthma on PCA risk. A recent meta-analysis of 14 clinical studies on asthma and PCA showed no association between them in the general population, whether Caucasian or Asian population by subgroup analysis.[47]

We also found that autoimmune hyperthyroidism and psoriatic arthropathies may act as potential protective factors against PCA. Due to the small number of cases of both diseases, prospective studies with larger sample sizes are needed.

Our study is currently the most comprehensive MR study to explore the association between autoimmunity-related diseases and PCA. However, it has several shortcomings. First, the GWAS data selected were of European ancestry, and the results of this study need to be further verified by demographic stratification before they can be generalized to other races. Second, the exposure variance explained by SNPs is small; therefore, a large sample size is required to ensure the robustness of the results. For some exposure data, the insignificance of the results may be false negatives owing to insufficient sample size, which lacks efficacy, such as in rheumatic myalgia. There are still some autoimmunity-related diseases for which MR analysis cannot be performed owing to the absence of appropriate GWAS data. Third, MR can only make rough judgments about potential causality; therefore, it is difficult to explore the underlying physiological mechanisms. Autoimmunity-related diseases represent a complex state of the human body, involving laborious biological mechanisms rather than a single biomarker signaling pathway. Further studies are required to explore the mechanisms underlying their association with cancer. Fourth, we did not have access to the raw data, so we could not conduct subgroup analysis; therefore, it is difficult to draw more detailed causal conclusions between different subtypes of autoimmunity-related disorders and different stages of prostate cancer. Our study could not predict recurrence or death owing to a lack of follow-up. Larger sample sizes and longer-term trials are required to verify these results.

In conclusion, this study suggests that autoimmunity-related disorders play an important role in the pathogenesis of PCA. Further research is needed to explore the underlying mechanisms of comorbidities at the molecular level. Additionally, validation of the initial Mendelian analysis results requires larger GWAS datasets in the future.

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Authors contribution

Peixian Chen and Yue Wang performed the literature search, drafted the manuscript, and contributed equally to the manuscript; Zhi Xiong and Tianlong Luo optimized data visualization; Yiming Lai1 and Haitao Zhong modified the format of the manuscript. Shirong Peng and Ruilin Zhuang investigated the background of the research; Kaiwen Li and Hai Huang reviewed and revised the article. All the authors critically revised and approved the final version of the manuscript.

Ethics statement

None.

Data availability statement

The datasets used in the current study are available from the corresponding author on reasonable request.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cpt.2024.03.002.

References

1. Pinsky PF, Parnes H. Screening for prostate cancer. *N Engl J Med*. 2023;388:1405–1414. https://doi.org/10.1056/NEJMcp2209151.
2. Kumar R, Sena LA, Denmeade SR, Kachhap S. The testosterone paradox of advanced prostate cancer: mechanistic insights and clinical implications. *Nat Rev Urol*. 2023;20:265–278. https://doi.org/10.1038/s41585-022-00686-y.
3. Liu JM, Yu CP, Chuang HC, Wu CT, Hsu RJ. Androgen deprivation therapy for prostate cancer and the risk of autoimmune diseases. *Prostate Cancer Prostatic Dis*. 2019;22:475–482. https://doi.org/10.1038/s41391-019-0130-9.
4. Burgess S, Small DS, Thompson SG. A review of instrumental variable estimators for mendelian randomization. *Stat Methods Med Res*. 2017;26:2333–2355. https://doi.org/10.1177/0962280215597579.
5. Smith GD, Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol*. 2003;32:1–22. https://doi.org/10.1093/ije/dyg070.
6. Davies NM, Holmes MV, Davey Smith G. Reading mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *BMJ*. 2018;362:k601. https://doi.org/10.1136/bmj.k601.
7. Valette K, Li Z, Bon-Baret V, et al. Prioritization of candidate causal genes for asthma in susceptibility loci derived from UK biobank. *Commun Biol*. 2021;4:700. https://doi.org/10.1038/s42003-021-02227-6.
8. Trynka G, Hunt KA, Bockett NA, et al. Dense genotyping identifies and localizes multiple common and rare variant association signals in celiac disease. *Nat Genet*. 2011;43:1193–1201. https://doi.org/10.1038/ng.998.
9. Ji SG, Juran BD, Mucha S, et al. Genome-wide association study of primary sclerosing cholangitis identifies new risk loci and quantifies the genetic relationship with inflammatory bowel disease. *Nat Genet*. 2017;49:269–273. https://doi.org/10.1038/ng.3745.
10. Forgetta V, Manousaki D, Istomine R, et al. Rare genetic variants of large effect influence risk of type 1 diabetes. *Diabetes*. 2020;69:784–795. https://doi.org/10.2337/db19-0831.
11. Bentham J, Morris DL, Graham DSC, et al. Genetic association analyses implicate aberrant regulation of innate and adaptive immunity genes in the pathogenesis of systemic lupus erythematosus. *Nat Genet*. 2015;47:1457–1464. https://doi.org/10.1038/ng.3434.

12. Ha E, Bae SC, Kim K. Large-scale meta-analysis across east asian and european populations updated genetic architecture and variant-driven biology of rheumatoid arthritis, identifying 11 novel susceptibility loci. *Ann Rheum Dis*. 2021;80:558–565. https://doi.org/10.1136/annrheumdis-2020-219065.
13. Cortes A, Hadler J, Pointon JP, et al. Identification of multiple risk variants for ankylosing spondylitis through high-density genotyping of immune-related loci. *Nat Genet*. 2013;45:730–738. https://doi.org/10.1038/ng.2667.
14. de Lange KM, Moutsianas L, Lee JC, et al. Genome-wide association study implicates immune activation of multiple integrin genes in inflammatory bowel disease. *Nat Genet*. 2017;49:256–261. https://doi.org/10.1038/ng.3760.
15. International Multiple Sclerosis Genetics Consortium. Multiple sclerosis genomic map implicates peripheral immune cells and microglia in susceptibility. *Science*. 2019;365:eaav7188. https://doi.org/10.1126/science.aav7188.
16. Eijsbouts C, Zheng T, Kennedy NA, et al. Genome-wide analysis of 53,400 people with irritable bowel syndrome highlights shared genetic pathways with mood and anxiety disorders. *Nat Genet*. 2021;53:1543–1552. https://doi.org/10.1038/s41588-021-00950-8.
17. Schumacher FR, Al Olama AA, Berndt SI, et al. Association analyses of more than 140,000 men identify 63 new prostate cancer susceptibility loci. *Nat Genet*. 2018;50:928–936. https://doi.org/10.1038/s41588-018-0142-8.
18. Larsson SC, Bäck M, Rees JMB, Mason AM, Burgess S. Body mass index and body composition in relation to 14 cardiovascular conditions in UK biobank: a mendelian randomization study. *Eur Heart J*. 2020;41:221–226. https://doi.org/10.1093/eurheartj/ehz388.
19. Burgess S, Bowden J, Fall T, Ingelsson E, Thompson SG. Sensitivity analyses for robust causal inference from mendelian randomization analyses with multiple genetic variants. *Epidemiology*. 2017;28:30–42. https://doi.org/10.1097/ede.0000000000000559.
20. Choi Y, Lee SJ, Spiller W, et al. Causal associations between serum bilirubin levels and decreased stroke risk: a two-sample mendelian randomization study. *Arterioscler Thromb Vasc Biol*. 2020;40:437–445. https://doi.org/10.1161/atvbaha.119.313055.
21. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from mendelian randomization between complex traits and diseases. *Nat Genet*. 2018;50:693–698. https://doi.org/10.1038/s41588-018-0099-7.
22. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through egger regression. *Int J Epidemiol*. 2015;44:512–525. https://doi.org/10.1093/ije/dyv080.
23. Hemani G, Zheng J, Elsworth B, et al. The mr-base platform supports systematic causal inference across the human phenome. *Elife*. 2018;7. https://doi.org/10.7554/eLife.34408.
24. Sanderson E, Davey Smith G, Windmeijer F, Bowden J. An examination of multivariable mendelian randomization in the single-sample and two-sample summary data settings. *Int J Epidemiol*. 2019;48:713–727. https://doi.org/10.1093/ije/dyy262.
25. Wheeler AM, Roul P, Yang Y, et al. Risk of prostate cancer in us veterans with rheumatoid arthritis. *Arthritis Care Res*. 2023;75:785–792. https://doi.org/10.1002/acr.24890.
26. England BR, Campany M, Sayles H, et al. Associations of serum cytokines and chemokines with the risk of incident cancer in a prospective rheumatoid arthritis cohort. *Int Immunopharm*. 2021;97:107719. https://doi.org/10.1016/j.intimp.2021.107719.
27. Clarke AE, Pooley N, Marjenberg Z, et al. Risk of malignancy in patients with systemic lupus erythematosus: systematic review and meta-analysis. *Semin Arthritis Rheum*. 2021;51:1230–1241. https://doi.org/10.1016/j.semarthrit.2021.09.009.
28. Song L, Wang Y, Zhang J, Song N, Xu X, Lu Y. The risks of cancer development in systemic lupus erythematosus (sle) patients: a systematic review and meta-analysis. *Arthritis Res Ther*. 2018;20:270. https://doi.org/10.1186/s13075-018-1760-3.
29. Ghaderi A. Ctla4 gene variants in autoimmunity and cancer: a comparative review. *Iran J Immun : IJI*. 2011;8:127–149. https://doi.org/ijiv8i3a1.
30. Bernatsky S, Ramsey-Goldman R, Gordon C, Clarke AE. Prostate cancer in systemic lupus erythematosus. *Int J Cancer*. 2011;129:2966–2969. https://doi.org/10.1002/ijc.25956.
31. Ward MM, Alehashemi S. Risks of solid cancers in elderly persons with osteoarthritis or ankylosing spondylitis. *Rheumatology*. 2020;59:3817–3825. https://doi.org/10.1093/rheumatology/keaa166.
32. Muller S, Hider SL, Belcher J, Helliwell T, Mallen CD. Is cancer associated with polymyalgia rheumatica? A cohort study in the general practice research database. *Ann Rheum Dis*. 2014;73:1769–1773. https://doi.org/10.1136/annrheumdis-2013-203465.
33. Ji J, Liu X, Sundquist K, Sundquist J, Hemminki K. Cancer risk in patients hospitalized with polymyalgia rheumatica and giant cell arteritis: a follow-up study in Sweden. *Rheumatology*. 2010;49:1158–1163. https://doi.org/10.1093/rheumatology/keq040.
34. Pedersen N, Duricova D, Elkjaer M, Gamborg M, Munkholm P, Jess T. Risk of extra-intestinal cancer in inflammatory bowel disease: meta-analysis of population-based cohort studies. *Am J Gastroenterol*. 2010;105:1480–1487. https://doi.org/10.1038/ajg.2009.760.
35. Burns JA, Weiner AB, Catalona WJ, et al. Inflammatory bowel disease and the risk of prostate cancer. *Eur Urol*. 2019;75:846–852. https://doi.org/10.1016/j.eururo.2018.11.039.
36. Ge Y, Shi Q, Yao W, Cheng Y, Ma G. The association between inflammatory bowel disease and prostate cancer risk: a meta-analysis. *Prostate Cancer Prostatic Dis*. 2020;23:53–58. https://doi.org/10.1038/s41391-019-0177-7.
37. Sfanos KS, Yegnasubramanian S, Nelson WG, De Marzo AM. The inflammatory microenvironment and microbiome in prostate cancer development. *Nat Rev Urol*. 2018;15:11–24. https://doi.org/10.1038/nrurol.2017.167.
38. Sfanos KS, Joshu CE. Ibd as a risk factor for prostate cancer: what is the link? *Nat Rev Urol*. 2019;16:271–272. https://doi.org/10.1038/s41585-019-0157-7.
39. Hu Z, Fu Y, Wang J, Li Y, Jiang Q. Association between multiple sclerosis and prostate cancer risk: a systematic review and meta-analysis. *Oncol Lett*. 2023;25:83. https://doi.org/10.3892/ol.2023.13669.
40. Ysrraelit MC, Correale J. Impact of andropause on multiple sclerosis. *Front Neurol*. 2021;12:766308. https://doi.org/10.3389/fneur.2021.766308.
41. 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;38:264–270. https://doi.org/10.2337/dc14-1996.
42. Kang J, Chen MH, Zhang Y, et al. Type of diabetes mellitus and the odds of gleason score 8 to 10 prostate cancer. *Int J Radiat Oncol Biol Phys*. 2012;82:e463–e467. https://doi.org/10.1016/j.ijrobp.2011.07.003.
43. Di Sebastiano KM, Pinthus JH, Duivenvoorden WCM, Mourtzakis M. Glucose impairments and insulin resistance in prostate cancer: the role of obesity, nutrition and exercise. *Obes Rev : Off J Int Assoc Study Obesity*. 2018;19:1008–1016. https://doi.org/10.1111/obr.12674.
44. Watts EL, Perez-Cornago A, Fensom GK, et al. Circulating insulin-like growth factors and risks of overall, aggressive and early-onset prostate cancer: a collaborative analysis of 20 prospective studies and mendelian randomization analysis. *Int J Epidemiol*. 2023;52:71–86. https://doi.org/10.1093/ije/dyac124.
45. Zitzmann M. Testosterone deficiency, insulin resistance and the metabolic syndrome. *Nat Rev Endocrinol*. 2009;5:673–681. https://doi.org/10.1038/nrendo.2009.212.
46. Severi G, Baglietto L, Muller DC, et al. Asthma, asthma medications, and prostate cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2010;19:2318–2324. https://doi.org/10.1158/1055-9965.Epi-10-0381.
47. Li W, Mao S, Tu M, et al. Asthma and the risk of prostate cancer. *J Cancer Res Therapeut*. 2018;14:S571–s575. https://doi.org/10.4103/0973-1482.176422.