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Causal Relationship and Potential Common Pathogenic Mechanisms Between Alopecia Areata and Related Cancer

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Objective: Alopecia areata (AA) is an autoimmune skin disease. Observational studies have reported an association between AA and cancer. However, the causal relationship between AA and cancer has not been reported. We employed a two-sample Mendelian randomization (MR) study to assess the causality between AA and 17 subtypes of cancers.

Methods: We employed a two-sample Mendelian randomization (MR) study to assess the causality between AA and 17 subtypes of cancers. AA and cancers' association genome-wide association study (GWAS) data were collected. The inverse variance weighted (IVW) method was utilized as the principal method in our Mendelian randomization (MR) study, with additional use of the MR-Egger, weighted median, simple mode, and weighted mode methods. After that, we explored the underlying biological mechanisms by Bioinformatic Analysis.

Results: According to our MR analysis, AA has a causal relationship with hepatic bile duct cancer (HBDC, (odds ratio [OR] = 0.944, 95% confidence interval [CI] = 0.896–0.994, *P*-value = 0.030) and colorectal cancer (CRC, OR = 0.981, 95% CI = 0.963–0.999, *P*-value = 0.046). AA could decrease the risk of HBDC and CRC. No causal link between AA and other subtypes of cancers was observed. No heterogeneity or pleiotropy was observed. Furthermore, disease-related genes were obtained, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis results showed that the set of genes associated with immunity-inflammatory signaling pathway.

Conclusion: This study provided new evidence of the relationship between AA with HBDC and CRC. AA may play a protective role in both HBDC and CRC progression. This could provide newer avenues for research in search of treatment for HBDC and CRC.

Keywords: alopecia areata, cancer, causal relationship, colorectal cancer, hepatic bile duct cancer, Mendelian randomization

Introduction

Alopecia areata (AA) is an autoimmune skin disorder where patients suffering from AA were characterized by hair loss in focal regions, such as the complete scalp, including eyelashes and eyebrows, or even any hair-bearing surface.[1–3] The clinical presentation of AA can range from small patches of hair loss to widespread involvement of the scalp or the entire body.[1,3] Statistically, AA has affected nearly 2% of the general population, regardless of ethnic groups, genders, and age-based groups.[1,4] While the exact pathogenesis of AA remains unclear, it is believed that the collapse of the immune privilege of the hair follicle caused by immunological mechanism plays a fundamental role in AA progression.[2] Genetic factors and environment factors (including immunology, oxidative stress, microbiome, and allergy) contribute to the pathogenesis of AA.[2,5,6] Traditional treatment options for AA mainly refer to the usage of corticosteroids (intralesional, topical or systemic), immunosuppressants such as methotrexate are supplementary treatments for recalcitrant and extensive AA.[7] Besides, Janus kinase (JAK) inhibitors, Tumor necrosis factor-α (TNF-α) inhibitors (such as adalimumab and etanercept) were considered as new treatment strategies for AA.[8–10] It is important to note that while treatments for

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AA are of limited efficacy or are associated with potential side effects, many patients experience unpredictable cycles of hair loss and regrowth, with some cases being persistent and extensive.[1,2]

Studies also reported that AA is associated with various other disorders. For instance, AA greatly impacts the quality of life for patients, lead to the development of psychological disorders such as anxiety and depression.[11] Atopic diathesis including asthma, atopic dermatitis, allergic rhinitis and allergic conjunctivitis were more prevalent in patients with AA compared with matched control subjects.[12] A systematic review indicated that patients with AA were more likely to suffer from thyroid diseases, psychiatric diseases, vitamin D deficiency, ophthalmic abnormalities.[13]

Mendelian randomization (MR) utilizes one or more genetic variants as instrumental variables (IVs) based on genome-wide association studies (GWAS). MR studies can infer the causal effects of exposure on an outcome. Recently, MR analysis also reported the causal relationship between AA and other diseases. For instance, MR analysis showed that AA was associated with an increased risk of myocardial infarction (MI).[14] Similarly, AA could causally increase the risk of major depression disorder (MDD) and anxiety.[15] However, to our knowledge, no study has yet investigated the causal effect of AA on the risk of cancer using Mendelian randomization. Our investigation aimed to explore the AA variants as instrumental variables for cancer risk utilizing two-sample MR, screen the gene sets and characteristic crosstalk genes of AA and related cancer.

Materials and Methods

Study Design

According to the MR framework (Figure 1), three key assumptions are included: (1) Relevance Assumption: Single nucleotide polymorphisms (SNPs) that are substantially linked to exposures (AA) are used as Instrumental variables (IVs). (2) Independence Assumption: These SNPs (IVs) should not show any correlation with the relevant confounding factor. (3) Exclusivity Assumption: These SNPs (IVs) should affect outcomes (different subtypes of cancers) only through its effect on exposure.[16–19]

Data Sources

We utilized summary data associated with AA and 17 subtypes of cancers from MRC Integrative Epidemiology Unit Open GWAS database (https://gwas.mrcieu.ac.uk). Accession numbers finn-b-L12_ALOPECAREATA for AA, 289 cases and 211,139 controls, information of different subtypes of cancers were detailed in Table 1, summary data were accessed from IEU Open GWAS project database (https://gwas.mrcieu.ac.uk). Our study was conducted by secondary analysis of

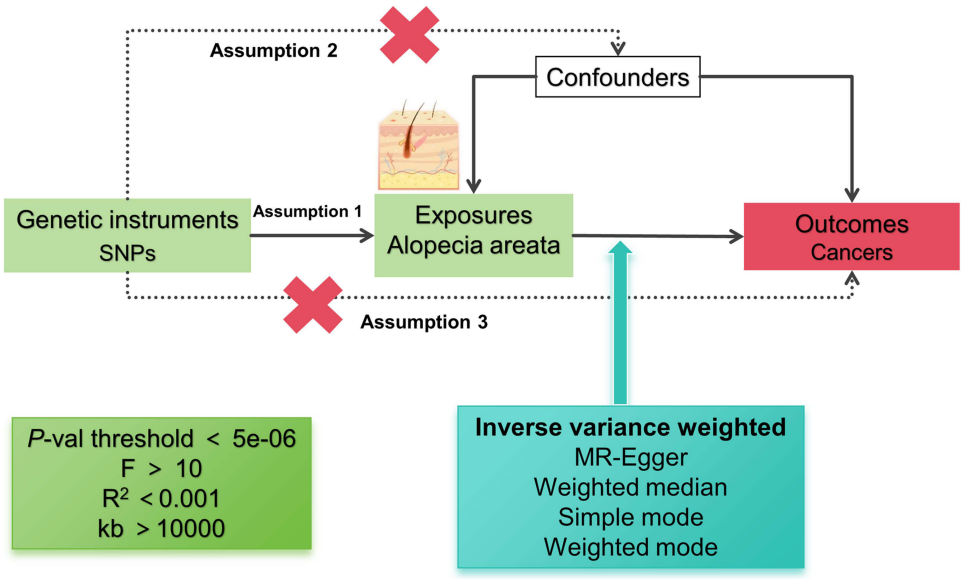

Figure 1 Flowchart schematic diagram followed by the MR analysis' principal of this study.

Table 1 Information of GWAS Summary Data Source Included in the Study

Trait	GWAS ID	Sample size	No. of SNPs	Year
Alopecia areata	**finn-b-L12_ALOPECAREATA**	**/**	**16,380,450**	**2021**
Hepatic bile duct cancer	**ebi-a-GCST90018803**	**476,091**	**24,196,592**	**2021**
Colorectal cancer	**ebi-a-GCST90018808**	**470,002**	**24,182,361**	**2021**
Breast cancer	ebi-a-GCST90018799	257,730	24,133,589	2021
Cervical cancer	ebi-a-GCST90018817	239,158	24,138,337	2021
Endometrial cancer	ebi-a-GCST90018838	240,027	24,135,295	2021
Esophageal cancer	ebi-a-GCST90018841	476,306	24,194,380	2021
Gastric cancer	ebi-a-GCST90018849	476,116	24,188,662	2021
Hepatic cancer	ebi-a-GCST90018858	475,638	24,194,938	2021
Lung cancer	ebi-a-GCST90018875	492,803	24,188,684	2021
Lymphoid and hematopoietic malignant neoplasms	finn-b-CD2_PRIMARY_LYMPHOID_HEMATOPOIETIC_EXALLC	/	16,380,350	2021
Ovarian cancer	ebi-a-GCST90018888	246,520	24,137,758	2021
Pancreatic cancer	ebi-a-GCST90018893	476,245	24,195,229	2021
Pharyngeal and laryngeal cancer	ebi-a-GCST90018898	355,564	19,083,781	2021
Prostate cancer	ebi-a-GCST90018905	211,227	24,119,306	2021
Skin cancer	ebi-a-GCST90018921	492,203	24,178,924	2021
Thyroid cancer	ebi-a-GCST90018929	491,974	24,198,226	2021
Urinary tract cancer	ukb-d-C_URINARY_TRACT	361,194	10,309,627	2018

Notes: Bold: Alopecia areata (Line 1) has a causal relationship with hepatic bile duct cancer (Line 2) and colorectal cancer (Line 3); /: Not applicable.

data from other studies, all participants or their family members have provided informed written consent in the original studies.

Instrumental Variables (IVs) Selection

Related IVs for MR analysis followed particular principles: SNPs should be associated with exposures at the locus-wide significance level: *P*-value <5e-06. In addition, linkage disequilibrium (LD) coefficient r^2 should be less than 0.001, not closely related (clumping window more than 10,000 kb) to ensure exposure instrument independence. We used the F statistic to measure the strength of the IVs, the values of F-statistics were more than 10.[16–19]

MR Analysis

Causal associations between AA and cancers were determined utilizing MR analysis. In the exposure-outcome analysis, we employed MR with more than two SNPs serving as IVs. Our MR analysis using each of the five methods: inverse variance-weighted (IVW) was performed as the primary statistical analysis method in our MR analysis for evaluating causal effects, besides, weighted median, and MR-Egger, simple mode, weighted mode were utilized.[16–19]

The heterogeneity of the chosen SNPs was evaluated using Cochrane's Q test, a *P*-value of more than 0.05 suggested the lack of heterogeneity. The random effects model was used once significant heterogeneity has been identified. We evaluated the possible bias from horizontal pleiotropy using the weighted median and MR-Egger regression in order to gauge the robustness of the IVW method. The MR-PRESSO (MR-Pleiotropy RESidual Sum and Outlier) test was used to appraise outliers that might have been influenced by horizontal pleiotropy. The causal-effect estimates for individual variants were displayed using Scatter plot. Thereafter, we performed a "leave-one-out" analysis to examine the stability of the results in the context of a single SNP's influence and presented the findings in a forest plot.[16–19]

All statistical analysis were conducted in R software (Version 4.3.2) using the TwoSampleMR package (Version 0.5.8). The statistical significance level is *P*-value <0.05. Pooled ORs (odds ratio) with 95% confidence interval (CI) were calculated.

Acquisition the Related Genes

Disease-related genes were obtained from The GeneCards database (https://www.genecards.org/), using the key word "alopecia areata" and causal related cancers. Intersection of the disease genes were used to obtain the crosstalk genes.

Enrichment Analysis of Crosstalk Genes

The R software packages "org.Hs.eg.db" and "clusterProfiler" were used to enrich the obtained crosstalk genes of AA and related cancers in the Gene Ontology (GO) categories of molecular function (MF), biological process (BP), and cellular component (CC). Thereafter, Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis were performed on the obtained crosstalk genes in AA and related cancers. Adjust *P*-value <0.05 was used as a filtering condition.

Results

Instrumental Variables

According to the quality control principle as mentioned, 12 SNPs related with AA were adopted as Instrumental variables (IVs). The SNPs included in the exposure data are detailed in Supplementary Table S1.

MR Analysis

We conducted the two-sample MR analysis between AA and 17 subtypes of cancers. The IVW MR analysis demonstrated that AA has a causal relationship with hepatic bile duct cancer (HBDC, OR = 0.944, 95% CI = 0.896–0.994, *P*-value = 0.030, Table 2) and colorectal cancer (CRC, OR = 0.981, 95% CI = 0.963–0.999, *P*-value = 0.046, Table 3), respectively. Interestingly, AA play protective roles in both HBDC and CRC. No causal association between AA and other cancers was observed (Figure 2). Using the MR-Egger, the relationship between AA and HBDC, CRC was visualized, respectively (Figure 3a and b).

Sensitivity Analysis

According to the analysis of Cochran's Q test, our IVW-MR analysis results demonstrated no evidence of heterogeneity among the reported results. Furthermore, the MR-Egger regression analysis results provided evidence that there exists no significant horizontal pleiotropy in our MR analysis, and MR-PRESSO analysis indicated that no outliers were identified (Table 4). The symmetric funnel plot (Figure 4) indicated no evidence of horizontal pleiotropy. We also conducted leave-one-out method to identify and delete abnormal instrumental variables (Figure 5). The results showed the robustness of our results. These results suggest that the MR analysis results were relatively stable.

Table 2 Causal Relationship Between AA and HBDC

Exposure	Outcome	Methods	*P*-val
AA	HBDC	Inverse variance weighted	0.030
		MR-Egger	0.142
		Weighted median	0.135
		Simple mode	0.267
		Weighted mode	0.180

Abbreviations: AA, Alopecia areata; HBDC, Hepatic bile duct cancer.

Table 3 Causal Relationship Between AA and CRC

Exposure	Outcome	Methods	*P*-val
AA	CRC	Inverse variance weighted	0.046
		MR-Egger	0.050
		Weighted median	0.196
		Simple mode	0.901
		Weighted mode	0.254

Abbreviations: AA, Alopecia areata; CRC, Colorectal cancer.

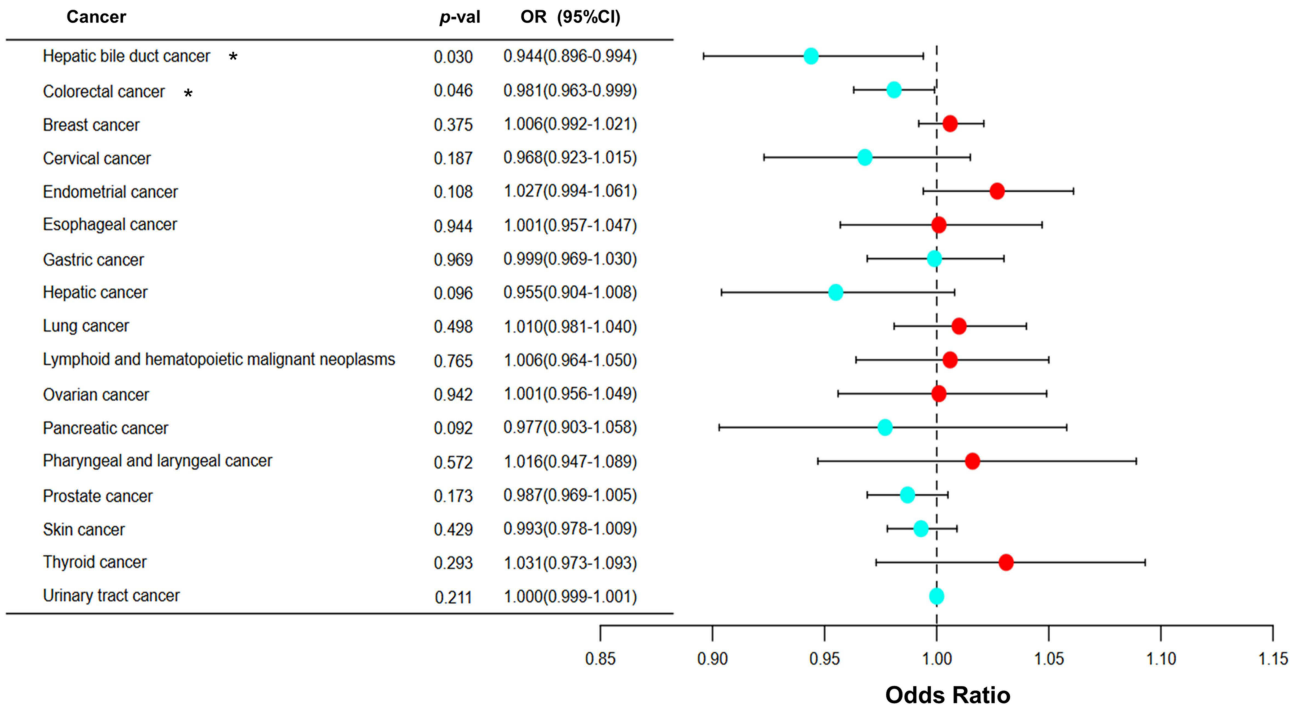

Figure 2 Forest plot of Mendelian randomization analysis for Alopecia areata on 17 subtypes of cancers risk. OR, odds ratio; CI, confidence interval; * *P*-value <0.05.

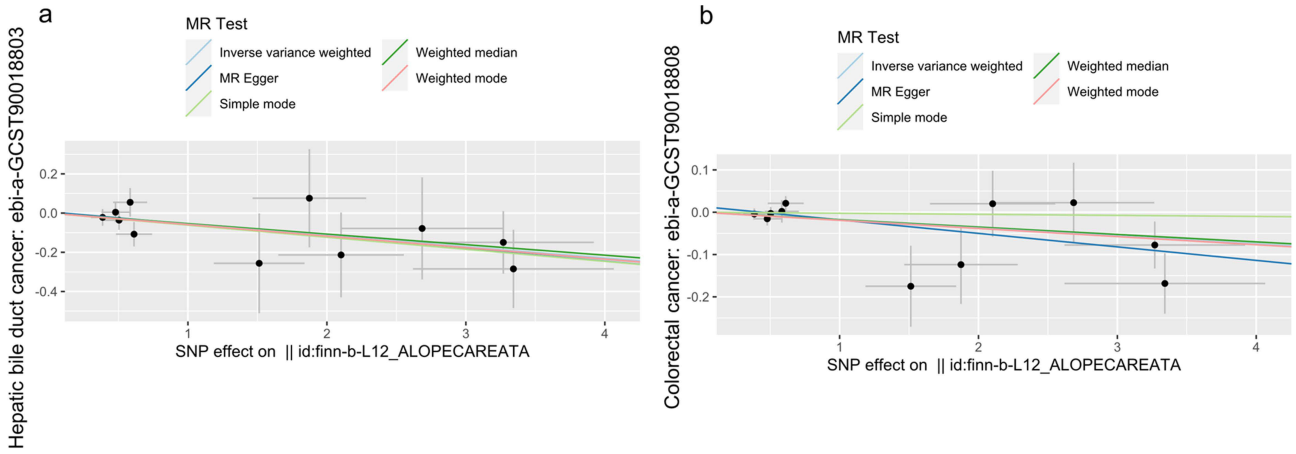

Figure 3 Scatter plots showing significant causal effects. (**a**) Alopecia areata on Hepatic bile duct cancer; (**b**) Alopecia areata on Colorectal cancer.

Reversed MR

We also conducted the reversed MR. We identified 11 SNPs from HBDC, 76 SNPs from CRC (detailed in supplementary Tables S2 and S3). No significant results were detected when AA was conducted as the outcome (Tables 5 and 6). These results indicated that HBDC or CRC has no causal impact on AA.

Table 4 Sensitivity Analysis of Our MR

Outcome	Q	*P*-value for Cochran Q test	Egger-intercept	*P*-value for MR-Egger intercept	*P*-value for MR-PRESSO Global test
HBDC	4.750	0.907	0.006	0.849	0.931
CRC	11.031	0.355	0.014	0.249	0.378

Abbreviations: HBDC, Hepatic bile duct cancer; CRC, Colorectal cancer.

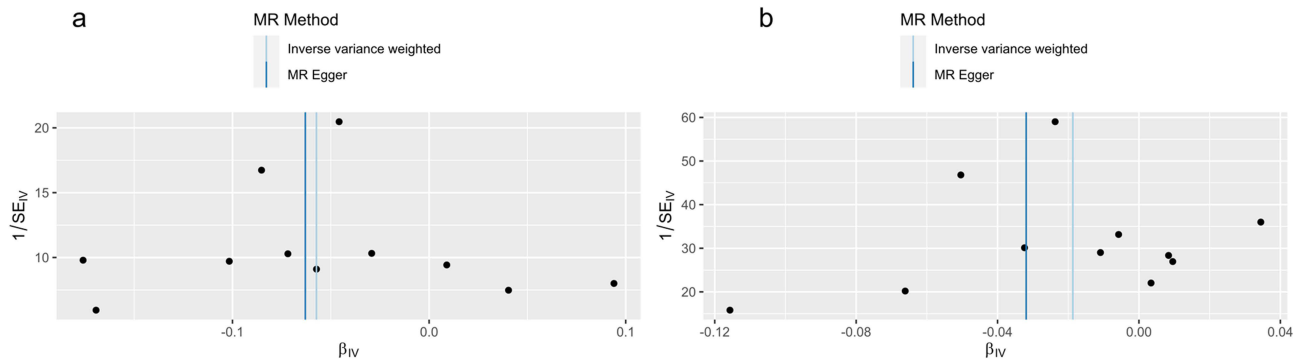

Figure 4 Funnel plot of our Mendelian randomization study. (**a**) Alopecia areata on Hepatic bile duct cancer; (**b**) Alopecia areata on Colorectal cancer.

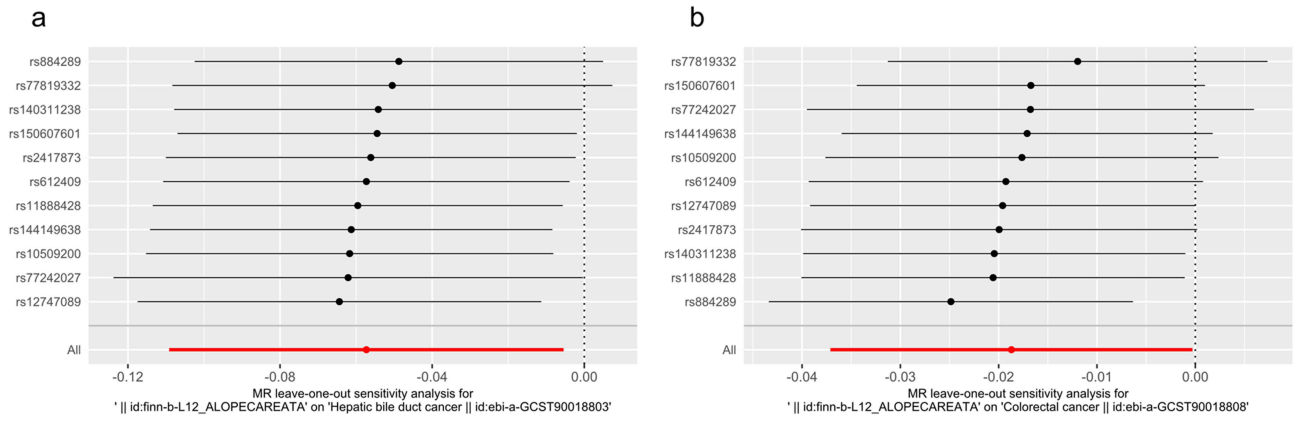

Figure 5 Results of "Leave-one-out" sensitivity analysis in our Mendelian randomization study. (**a**) Alopecia areata on Hepatic bile duct cancer; (**b**) Alopecia areata on Colorectal cancer.

Crosstalk Genes and Enrichment Analysis

A total of 613 AA disease genes, 4892 hBDC disease genes, 12,806 CRC disease genes were obtained from the GeneCard, respectively. As shown in Figure 6a, considering the intersection of these diseases, 287 intersecting genes were obtained (Table S4 for details).

Table 5 Reverse Causality Between HBDC and AA

Exposure	Outcome	Methods	*P*-val
HBDC	AA	Inverse variance weighted	0.523
		MR-Egger	0.919
		Weighted median	0.996
		Simple mode	0.269
		Weighted mode	0.856

Abbreviations: AA, Alopecia areata; HBDC, Hepatic bile duct cancer.

Table 6 Reverse Causality Between CRC and AA

Exposure	Outcome	Methods	*P*-val
CRC	AA	Inverse variance weighted	0.688
		MR-Egger	0.587
		Weighted median	0.679
		Simple mode	0.535
		Weighted mode	0.577

Abbreviations: AA, Alopecia areata; CRC, Colorectal cancer.

GO enrichment results showed that the set of genes associated with inflammatory response, immune response, positive regulation of interleukin-6, interleukin-8, interleukin-10, interleukin-12 production, positive regulation of T cell proliferation, positive regulation of inflammatory response, the set of genes related to immune inflammation were significantly enriched among the crosstalk genes of AA, HBDC and CRC, as shown in Figure 6b-d. The KEGG enrichment results showed that Cytokine–cytokine receptor interaction, Th17 cell differentiation, Toll-like receptor signaling pathway, Janus kinase (JAK) signal transducer and activator of transcription (JAK-STAT) pathway signaling pathway, Intestinal immune network for IgA production, Tumor necrosis factor (TNF) signaling pathway were significantly enriched among the crosstalk genes of AA and causal related cancers, as shown in Figure 6e, Table S5 for details.

Discussion

We conducted a bidirectional MR analysis to investigate the causal relationship between AA and 17 subtypes of cancers. Our results showed that AA has a causal effect on HBDC and CRC, in contrast, HBDC or CRC has no causal impact on AA. Furthermore, these results provided evidence for a protective effect of AA on HBDC and CRC risk. To the best of our knowledge, this MR analysis is the first to investigate the causal relationship between AA and cancers.

HBDC (intrahepatic Cholangiocarcinoma, iCCA) accounts for 2% of all malignancies.[20] Anatomically, HBDC arises from the epithelium of the bile ducts (BD) and can involve any part of the biliary tract.[20,21] HBDC is the second most common cause of primary liver cancer, after hepatocellular carcinoma (HCC).[22] Surgical resection is still the possible curative therapy for HBDC, while the anatomical location influences the surgical techniques employed.[22] Radiotherapy in selected cases, and systemic chemotherapy also play a significant role in both curative and palliative cohort.[22,23] Generally, the prognosis of HBDC is poor, accordingly, one-year survival for HBDC was 25% and 5-year survival was 5% in Europe.[23]

Colorectal cancer (CRC) accounts for about 10% of all diagnosed cancers and cancer-related deaths worldwide each year.[24,25] It is the second most common cancer in women and the third most common in men. Women have a lower incidence and mortality rate compared to men, with rates approximately 25% lower.[25] The incidence of CRC worldwide is predicted to increase to 2.5 million new cases in 2035.[25,26] Risk factors such as obesity, lack of physical exercise, and smoking contribute to the increased risk of developing CRC. Treatments for CRC include endoscopic resection (for some early cancers) and surgical local excision, radiotherapy and systemic therapy, such as chemotherapy, targeted therapy, and immunotherapy.[25,27]

MR analysis has reported several factors associated with HBDC or CRC. Ulcerative colitis (UC) patients could increase the incidences of HBDC,[28] in addition, specific gut microbiota and metabolites have causal relationship with HBDC.[29] Living habits were also demonstrated to have causal impact on liver cancer: sleep duration has a negative correlation with HBDC, in contrast, there was a positive correlation found between insomnia and nap during the day with HBDC.[30] Likewise, MR analysis also indicated alcohol consumption, higher body mass index (BMI), low 25-hydroxyvitamin D could increase the risk of CRC.[31–33]

Observational studies have reported the relationship between AA and cancers.[34,35] Accordingly, AA decreased the risk of nonmelanoma skin cancer and melanoma.[34] Additionally, liver cancer, uterine, and cervix cancer were also significantly lower in patients with AA. In contrast, AA patients were more likely to suffer from lymphoma, breast cancer, kidney, and urinary bladder cancer.[35] However, our MR study did not find the causal relationship between AA and skin cancer, breast cancer, cervix cancer, lymphoma or urinary bladder cancer. Interestingly, a recent systematic review and meta-analysis conducted by *Sophia Ly* et al investigated the comorbid conditions associated with AA. The findings indicated that AA may serve as a protective factor against specific types of cancer, as individuals with AA demonstrated reduced odds of developing colorectal cancer (odds ratio [OR] 0.61, 95% confidence interval [CI] 0.42–0.89) and hepatocellular carcinoma (OR 0.37, 95% CI 0.25–0.56) in comparison to healthy control subjects. These outcomes provide additional corroboration for our findings.[36]

To our known, no studies reported the relationship between AA and HBDC or CRC, our MR analysis uncovered new evidence suggesting the potential link between AA and these two cancers. Immune-related factors may be potential explanations for the protective role of AA in cancer progression. As mentioned, the pathophysiology of AA is not fully

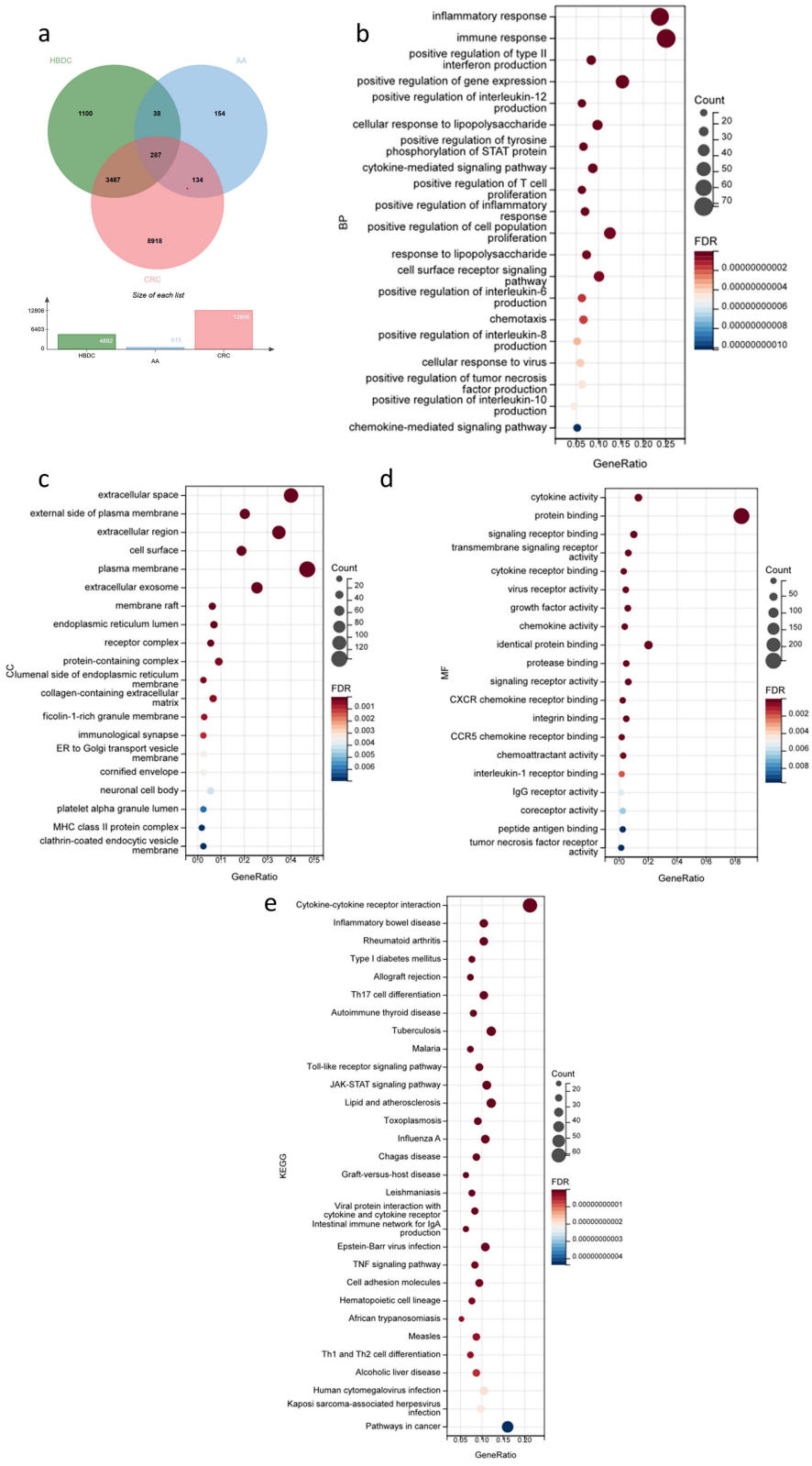

Figure 6 Disease genes and enrichment analysis. (**a**) intersecting genes between AA and causal related cancers; (**b**) biological process (BP); (**c**) cellular component (CC); (**d**) molecular function (MF); (**e**) Kyoto Encyclopedia of Genes and Genomes (KEGG) Enrichment analysis. AA= Alopecia areata. HBDC= Hepatic bile duct cancer. CRC= Colorectal cancer.

understood, while breaking down of the immune privilege of the hair follicles followed by autoimmune attack was believed to be the leading cause of AA.[35,37] On the other hand, upregulation of NKG2D ligands (NKG2DLs) compared with the infiltration of cytotoxic subset of CD8+NKG2D+ T cells in AA patient is the major pathogenesis of AA.[35,38] NKG2D and its ligand are known for their protective role in tumor immune surveillance, combined with the immune defense against tumors effect achieved by NK cells.[39] In our *Enrichment Analysis*, we also find immune-related inflammation was significantly enriched among the crosstalk genes of AA, HBDC and CRC. It should also be noted that, we also find that Th17 cell differentiation, Toll-like receptor signaling pathway, JAK-STAT signaling pathway, Intestinal immune network for IgA production, TNF signaling pathway were significantly enriched among the crosstalk genes, these pathways were related to immunity-inflammation procedure, regulating autoimmunity and cancer.[40–42] Meanwhile, the mechanism of how AA decreased the risk of HBDC and CRC remains uncertain.

There are several limitations to our study. First, due to the original GWAS statistics, we were unable to divide the cohorts or perform subgroup analyses. Second, our analysis only included individuals of the European population. Although using a single European population to investigate causal relationships can minimize population stratification bias, it is important to interpret these findings with caution regarding their applicability to other populations. Further research is required on the mechanism of how AA decreased HBDC and CRC risk.

Conclusion

In conclusion, our MR study has provided the first-ever evidence that AA has a causal impact on HBDC and CRC, AA decreased the risk of both HBDC and CRC. Besides, our results do not support a causal association between AA and other subtypes of cancers. Further studies focusing on AA may provide newer avenues for research in search of treatment targeted therapy in the treatment of HBDC and CRC.

Abbreviations

AA, Alopecia Areata; HBDC, Hepatic bile duct cancer; CRC, Colorectal cancer; MR, Mendelian randomization; IVW, Inverse-variance weighted; SNP, Single nucleotide polymorphism; IVs, Instrumental variables; GWAS, Genome-wide association study; LD, Linkage disequilibrium; WM, Weighted median; OR, Odds ratio; CI, Confidence interval; JAK-STAT, Janus kinase (JAK) signal transducer and activator of transcription; UC, Ulcerative colitis; BMI, body mass index.

Data Sharing Statement

No original data were generated in the present study. The datasets mentioned in this article are publicly available. Details see Supplementary Tables.

Ethics Statement

This study is exempt from ethical review as per Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Beings (National Science and Technology Ethics Committee, China). The exemption is based on the use of non-harmful, non-sensitive data from open, legal databases.

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Disclosure

The authors declare that they have no competing interests.

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