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Autoimmune thyroiditis and pan-cancer risk: A comprehensive Mendelian randomization study

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Abstract

Introduction: Autoimmune thyroiditis (AIT), clinically termed Hashimoto's thyroiditis (HT), is a chronic autoimmune condition characterized by progressive immune-mediated degeneration of thyroid tissue. The association between AIT and cancer risk, particularly thyroid cancer, remains controversial.

Objective: This study is aimed to investigate potential causal associations between AIT/HT and thyroid cancers or extra-thyroidal cancers comprehensively.

Methods: To clarify this uncertainty, we employed Mendelian randomization (MR) analysis to evaluate causal associations between genetic predisposition to AIT and pan-cancer risk, including subtypes of thyroid cancer and extra-thyroidal malignancies. Summary statistics were pooled from comprehensive genome-wide studies, including two independent AIT/HT datasets, 10 thyroid neoplasm datasets, and 33 extra-thyroidal cancer datasets. Bidirectional two-sample MR analyses were conducted to mitigate confounding and reverse causation. Quality control was reinforced through sensitivity analyses.

Results: Contrary to previous observational studies, our study found no genetically supported causal link between AIT/HT and the development of thyroid carcinoma. However, elevated risks of non-Hodgkin lymphoma, primary lymphoid/hematopoietic malignancies, testicular cancer, and brain cancer might be associated with AIT/HT. Sensitivity analyses confirmed the robustness of these results, although some associations exhibited heterogeneity or pleiotropy.

Conclusion: These findings reveal tissue-specific effects of thyroid autoimmunity on cancer development, suggesting distinct biological pathways beyond thyroid malignancies. This study provides genetic evidence that refines cancer risk assessment in patients with AIT/HT and emphasizes the need for further mechanistic research to elucidate underlying biological processes.

Keywords: Autoimmune thyroiditis; Mendelian randomization analysis; Thyroid cancer; Pan-cancer risk; Hashimoto's thyroiditis

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1. Introduction

Chronic lymphocytic thyroiditis, or autoimmune thyroiditis (AIT), clinically termed Hashimoto's thyroiditis (HT), is characterized by progressive autoimmune-mediated

damage to the thyroid gland, leading to follicular cell destruction and eventual fibrosis.[1] The pathogenesis involves a loss of immune tolerance to thyroid-specific antigens, such as thyroid peroxidase (TPO) and thyroglobulin (TG), leading to the production of autoantibodies (anti-TPO and anti-TG) and chronic inflammation. Over time, this immune-mediated damage impairs thyroid hormone synthesis, frequently resulting in hypothyroidism, a condition affecting a significant proportion of patients with long-standing AIT.[1] Epidemiologically, AIT is the most common autoimmune disease worldwide, with prevalence rates ranging from 0.1% to 5% in Western populations. A notable feature of AIT is its strong female predilection; women are 5–10 times more likely to develop the condition than men, suggesting a potential role for hormonal and genetic factors in its pathogenesis.[1] Symptoms of hypothyroidism include fatigue, weight gain, cold intolerance, dry skin, hair loss, muscle aches, constipation, depression, cognitive dysfunction, menstrual irregularities, bradycardia, and elevated cholesterol levels. At present, hormone replacement therapy (i.e., levothyroxine) can effectively manage hypothyroidism; however, the underlying chronic inflammation of the thyroid remains untreated, potentially creating a microenvironment favorable to carcinogenesis. This may partly explain the observed epidemiological associations between AIT and thyroid cancer, as well as other malignancies.[2]

Previous studies have examined possible associations between AIT and various cancer types, with particular focus on thyroid cancer due to their frequent clinical co-occurrence. As the most common endocrine-related cancer globally, thyroid malignancies are predominantly of papillary thyroid carcinoma (PTC) histology, comprising 80–90% of all thyroid cancers.[3] Clinically, AIT is often observed alongside PTC, yet the nature of this relationship remains debated in the medical community. A meta-analysis aggregating data from 64,628 subjects across 36 studies found a statistically significant association between AIT and PTC, as well as a link between AIT and thyroid lymphoma.[4] Several subsequent studies have consistently demonstrated that patients with AIT have an increased risk of developing PTC.[5,6] Beyond thyroid malignancies, AIT has also been implicated in an elevated risk of other cancers, including hematopoietic and lymphoid malignancies,[7] breast cancers,[8] lung cancers,[9] gastrointestinal cancers,[10] and urogenital cancers.[11] However, scientific consensus remains elusive. Some well-designed studies have failed to establish a clear connection between AIT and thyroid cancer or other cancers, with researchers attributing observed associations to detection bias or shared genetic risk factors rather than a direct causal relationship.[7,12,13] This ongoing controversy highlights the need for further large-scale, prospective studies incorporating molecular profiling to better understand the complex interplay between AIT and carcinogenesis.

While conventional cohort studies have provided valuable insights, they are inherently susceptible to confounding variables, including shared environmental exposures, medication effects, and comorbidities, which complicate efforts to determine whether observed correlations reflect causal relationships. Furthermore, issues such as reverse causality (e.g., undiagnosed cancer influencing thyroid autoimmunity) and selection bias further hinder the interpretation of findings. To address these limitations and investigate the causal relationship between AIT and pan-cancer risk from a genetic point of view, we employed Mendelian randomization (MR) analysis.[14] This method leverages the random assortment of alleles during meiosis, akin to a natural randomized controlled trial, and minimizes confounding from environmental factors. MR analysis addresses key limitations of observational studies, including confounding factors, reverse causality, and sampling bias, thereby offering a more rigorous and reliable framework for causal inference.[14] MR offers several advantages over traditional observational designs: (i) it is less susceptible to reverse causation, as genetic variants are fixed at conception and precede disease onset; (ii) it minimizes confounding by lifestyle or environmental factors; and (iii) it provides more reliable estimates of causal effects by using genetic instruments not influenced by disease processes. In the present study, we conducted bidirectional two-sample MR analyses to evaluate the effect of genetic predisposition to AIT/HT on the susceptibility to 37 cancer types. Thyroid cancers were analyzed both as a unified category and stratified by histological subtypes (papillary, follicular, and medullary carcinomas), together with 33 extra-thyroidal malignancies affecting multiple organ systems. By utilizing publicly available genome-wide association study (GWAS) meta-analysis data from large consortia, we were able to maximize statistical power and enhance the robustness of our causal inference. This approach enabled us not only to assess whether AIT contributes to cancer risk but also to explore the reverse hypothesis that genetic predisposition to certain cancers might influence AIT development, thereby providing a comprehensive view of the complex interplay between autoimmunity and oncogenesis.

2. Methods

2.1. Study design

Our analytical strategy is visually summarized in Figure 1, which outlines the comprehensive methodological

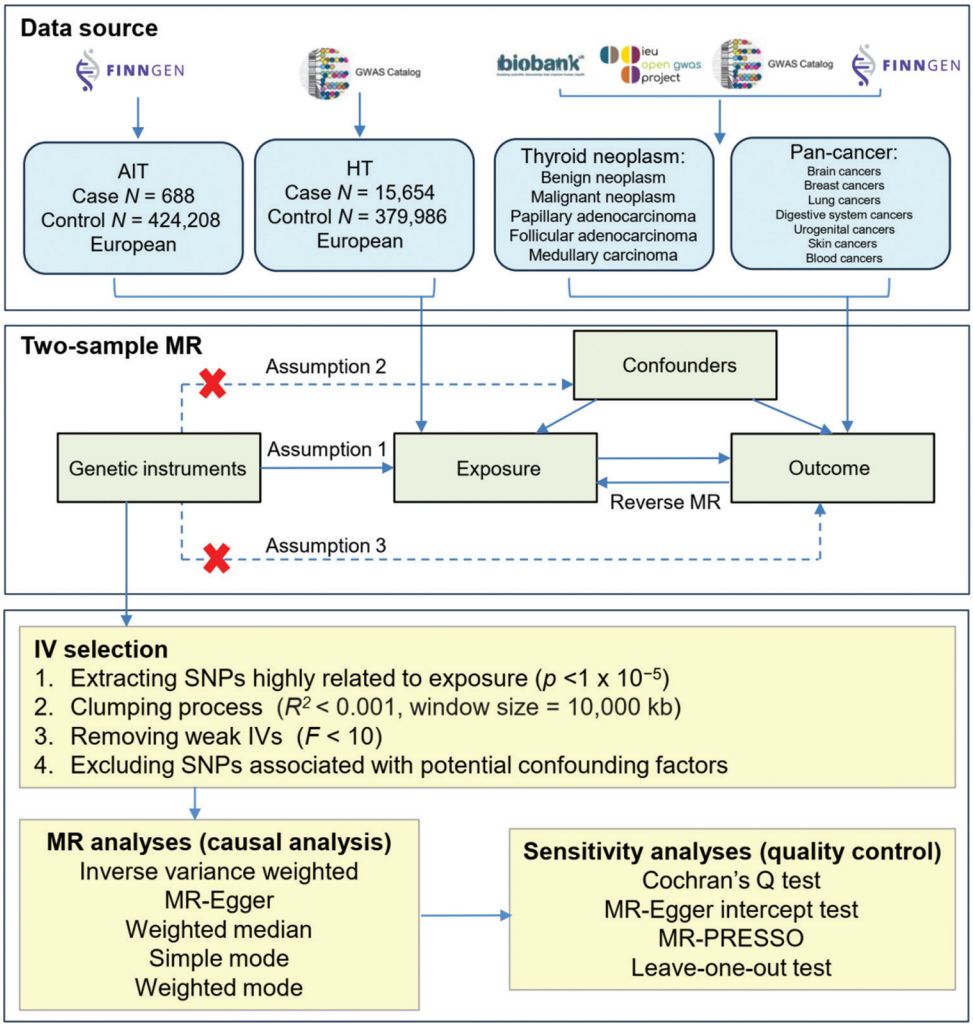

Figure 1. Flowchart of the study design. We performed a bidirectional two-sample Mendelian randomization (MR) analysis to assess causal relationships between autoimmune thyroiditis (AIT)/Hashimoto's thyroiditis (HT) and pan-cancer risk. Instrumental variables (IVs) were selected based on genome-wide significance, excluding single-nucleotide polymorphisms (SNPs) in linkage disequilibrium, weak IVs, or potential confounders. The primary analytical method was inverse-variance weighted, supplemented by MR-Egger, weighted median, and mode-based methods. Sensitivity analyses were conducted to evaluate heterogeneity (Cochran's *Q* test), horizontal pleiotropy (MR-Egger intercept, MR-Pleiotropy RESidual Sum and Outlier [PRESSO]), and the influence of individual SNPs (leave-one-out analysis).

framework employed in this investigation. We performed a two-sample MR analysis to explore the potential causal relationship between AIT and the susceptibility of 37 different cancer types. This analysis encompassed thyroid cancer (examined both collectively and by its three principal histological subtypes: papillary, follicular, and medullary carcinomas), along with 33 extra-thyroidal cancers representing diverse anatomical sites and pathological classifications. To enhance the validity of our findings and address potential methodological limitations, we also performed a bidirectional MR analysis, which included both a forward analysis (assessing the potential causal effect of AIT on cancer risk) and a reverse analysis (examining whether genetic predisposition to cancer might influence AIT development). The reverse MR analysis served two critical purposes: (i) to evaluate and mitigate potential reverse causation bias that could affect our primary findings; and (ii) to provide a more comprehensive understanding of the complex interrelationship between AIT and oncogenesis. The methodological robustness of our MR framework relies on three foundational assumptions, each of which was carefully evaluated throughout our analysis: (i) the relevance assumption – ensuring that all selected genetic variants serving as instrumental variables (IVs) were strongly and reliably associated with AIT; (ii) the independence assumption – confirming that these IVs were not associated with known confounders of the AIT–cancer relationship, as verified through sensitivity

analyses; and (iii) the exclusion restriction assumption – verifying that the genetic variants influenced cancer risk exclusively through their association with AIT, and not through alternative biological pathways. This study was conducted in full compliance with the Strenghtening the Reporting of Observational studies in Epidemiology-MR guidelines,[15] ensuring transparency, methodological rigor, and adherence to best practices in the reporting of MR analyses. This included detailed documentation of genetic instrument selection criteria, statistical methods for causal estimation, sensitivity analyses, and comprehensive reporting of all analytical steps.

2.2. GWAS datasets

The GWAS datasets used for the MR analyses in our study are summarized in Table 1. The dataset for AIT was obtained from the latest release (R12) of the FinnGen consortium's GWAS summary statistics (accessible at https://www.finngen.fi/en), which provides comprehensive data from large-scale biobank studies.[16] AIT is defined as: "An inflammatory disease of the thyroid gland caused by autoimmune responses leading to lymphocytic infiltration of the gland. It is characterized by the presence of circulating thyroid antigen-specific T-cells and thyroid autoantibodies. Clinical manifestations can range from hypothyroidism to thyrotoxicosis, depending on the type of autoimmune thyroiditis." An additional dataset for HT was obtained from the Integrative Epidemiology Unit (IEU) Open GWAS project (dataset: ebi-a-GCST90018855).[17] For thyroid neoplasms, we integrated 10 distinct GWAS datasets covering the full spectrum of thyroid tumor pathology, including: (i) benign thyroid neoplasms;

Table 1. Summary of GWAS datasets used in bidirectional Mendelian randomization analyses

GWAS ID	Study/Consortium, year	Trait	No. of cases	No. of controls	Sample size
Autoimmune thyroiditis					
finngen_R12_E4_THYROIDITAUTOIM	Kurki *et al.*, 2024[16]	Autoimmune thyroiditis	688	424,208	424,896
ebi-a-GCST90018855	Sakaue *et al.*, 2021[17]	Hashimoto's thyroiditis	15,654	379,986	395,640
Neoplasm of thyroid					
finngen_R12_CD2_BENIGN_THYROID	Kurki *et al.*, 2024[16]	Benign neoplasm of thyroid	1,184	499,164	500,348
finngen_R12_C3_THYROID_GLAND_EXALLC	Kurki *et al.*, 2024[16]	Malignant neoplasm of thyroid	2,859	378,749	381,608
finngen_R12_C3_THYROID_PAPILLARY_ADENO_EXALLC	Kurki *et al.*, 2024[16]	Papillary adenocarcinoma of thyroid	2400	378749	381149
finngen_R12_C3_THYROID_FOLLICULAR_EXALLC	Kurki *et al.*, 2024[16]	Follicular adenocarcinoma of thyroid	351	378749	379100
finngen_R12_C3_THYROID_MEDULLARY_EXALLC	Kurki *et al.*, 2024[16]	Medullary carcinoma of thyroid	72	378749	378821
ebi-a-GCST90018929	Sakaue *et al.*, 2021[17]	Thyroid cancer	1,054	490,920	491,974
ebi-a-GCST90013863	Mbatchou *et al.*, 2021[19]	Thyroid cancer (Firth correction)	617	407,129	407,746
ebi-a-GCST90013867	Mbatchou *et al.*, 2021[19]	Thyroid cancer (SPA correction)	617	407,129	407,746
ieu-a-1082	Köhler *et al.*, 2013[18]	Thyroid cancer	649	431	1,080
C3_THYROID_GLAND.gwas.imputed_v3.both_sexes	Sudlow *et al.*, 2015[20]	Malignant neoplasm of thyroid	394	360,800	361,194
Cancers, except thyroid					
finngen_R12_C3_ADRENAL_GLAND_EXALLC	Kurki *et al.*, 2024[16]	Malignant neoplasm of adrenal gland	242	378,749	378,991
finngen_R12_C3_ANUS_ANALCANAL_EXALLC	Kurki *et al.*, 2024[16]	Malignant neoplasm of anus and anal canal	405	378,749	379,154
finngen_R12_C3_BRAIN_EXALLC	Kurki *et al.*, 2024[16]	Malignant neoplasm of brain	1,894	378,749	380,643
finngen_R12_C3_HEAD_AND_NECK_EXALLC	Kurki *et al.*, 2024[16]	Malignant neoplasm of head and neck	3,942	378,749	382,691
finngen_R12_C3_ORALCAVITY_EXALLC	Kurki *et al.*, 2024[16]	Malignant neoplasm of oral cavity	1,614	378,749	380,363
finngen_R12_C3_BONE_CARTILAGE_EXALLC	Kurki *et al.*, 2024[16]	Malignant neoplasm of bone and articular cartilage	648	378,749	379,397

(Cont'd)

Table 1. ***(Continued)***

GWAS ID	Study/Consortium, year	Trait	No. of cases	No. of controls	Sample size
finngen_R12_C3_BREAST_ERNEG_EXALLC	Kurki *et al*., 2024[16]	Malignant neoplasm of breast, ER-negative	9,724	221,705	231,429
finngen_R12_C3_BREAST_ERPLUS_EXALLC	Kurki *et al*., 2024[16]	Malignant neoplasm of breast, ER-positive	14,540	221,705	236,245
finngen_R12_C3_BREAST_EXALLC	Kurki *et al*., 2024[16]	Malignant neoplasm of breast	24,270	222,078	246,348
finngen_R12_C3_BRONCHUS_LUNG_EXALLC	Kurki *et al*., 2024[16]	Malignant neoplasm of bronchus and lung	9,639	378,749	388,388
finngen_R12_C3_LUNG_NONSMALL_EXALLC	Kurki *et al*., 2024[16]	Non-small cell lung cancer	6,446	378,749	385,195
finngen_R12_C3_URINARY_TRACT_EXALLC	Kurki *et al*., 2024[16]	Malignant neoplasm of urinary organs	4,535	378,749	383,284
finngen_R12_C3_BLADDER_EXALLC	Kurki *et al*., 2024[16]	Malignant neoplasm of bladder	4,852	378,749	383,601
finngen_R12_C3_KIDNEY_ NOTRENALPELVIS_EXALLC	Kurki *et al*., 2024[16]	Malignant neoplasm of kidney, except renal pelvis	3,926	378,749	382,675
finngen_R12_C3_CERVIX_UTERI_EXALLC	Kurki *et al*., 2024[16]	Malignant neoplasm of cervix uteri	878	222,078	222,956
finngen_R12_C3_CORPUS_UTERI_EXALLC	Kurki *et al*., 2024[16]	Malignant neoplasm of corpus uteri	3,490	222,078	225,568
finngen_R12_C3_OVARY_EXALLC	Kurki *et al*., 2024[16]	Malignant neoplasm of ovary	2,339	222,078	224,417
finngen_R12_C3_PROSTATE_EXALLC	Kurki *et al*., 2024[16]	Malignant neoplasm of prostate	20,368	15,671	177,039
finngen_R12_C3_TESTIS_EXALLC	Kurki *et al*., 2024[16]	Malignant neoplasm of testis	687	156,671	157,358
finngen_R12_C3_STOMACH_EXALLC	Kurki *et al*., 2024[16]	Malignant neoplasm of stomach	2,296	378,749	381,045
finngen_R12_C3_BILIARY_GALLBLADDER_ EXALLC	Kurki *et al*., 2024[16]	Malignant neoplasm of intrahepatic ducts, biliary tract and gallbladder	2,298	378,749	381,047
finngen_R12_C3_PANCREAS_EXALLC	Kurki *et al*., 2024[16]	Malignant neoplasm of pancreas	3,139	378,749	381,888
finngen_R12_C3_COLON_ADENO_EXALLC	Kurki *et al*., 2024[16]	Colon adenocarcinoma	4,478	378,749	383,227
finngen_R12_C3_COLON_EXALLC	Kurki *et al*., 2024[16]	Malignant neoplasm of colon	7,698	378,749	386,447
finngen_R12_C3_COLORECTAL_ADENO_ EXALLC	Kurki *et al*., 2024[16]	Colorectal adenocarcinoma	7,876	378,749	386,625
finngen_R12_C3_COLORECTAL_EXALLC	Kurki *et al*., 2024[16]	Colorectal cancer	11,790	378,749	390,539
finngen_R12_C3_RECTUM_EXALLC	Kurki *et al*., 2024[16]	Malignant neoplasm of rectum	4,844	378,749	383,593
finngen_R12_C3_SMALL_INTESTINE_EXALLC	Kurki *et al*., 2024[16]	Malignant neoplasm of small intestine	1,034	378,749	379,783
finngen_R12_C3_SKIN_EXALLC	Kurki *et al*., 2024[16]	Malignant neoplasm of skin	34,177	378,749	412,926
finngen_R12_C3_MELANOMA_EXALLC	Kurki *et al*., 2024[16]	Malignant melanoma	6,925	378,368	385,293
finngen_R12_C3_CLL_EXALLC	Kurki *et al*., 2024[16]	Chronic lymphocytic leukemia and small lymphocytic leukemia	935	378,742	379,677
finngen_R12_CD2_PRIMARY_LYMPHOID_ HEMATOPOIETIC_EXALLC	Kurki *et al*., 2024[16]	Primary lymphoid and hematopoietic malignant neoplasms	9,960	378,749	388,709
finngen_R12_C3_NONHODGKIN_EXALLC	Kurki *et al*., 2024[16]	Non-Hodgkin lymphoma	5,225	378,749	383,974

Abbreviations: GWAS: Genome-wide association study; ER: Estrogen receptor; SPA: Saddlepoint approximation; UK: United Kingdom.

(ii) malignant thyroid neoplasms; and (iii) the three major histological subtypes (PTC, follicular adenocarcinoma, and medullary carcinoma). These datasets were carefully selected from three major genetic resources: the FinnGen consortium (R12), the IEU Open GWAS project, and the United Kingdom Biobank Project,[17-20] ensuring comprehensive coverage of thyroid cancer genetics. Our analysis of extra-thyroidal malignancies incorporated 33 rigorously curated GWAS datasets representing cancers across nine anatomical systems, including neuroendocrine cancers, neurological cancers, skeletal cancers, mammary cancers, respiratory cancers, urogenital cancers, gastrointestinal cancers, cutaneous cancers, and hematologic cancers. All original studies contributing to these GWAS resources obtained appropriate institutional ethics approval and documented participant consent. Our secondary analysis of anonymized summary-level data complied with all relevant data protection regulations and institutional policies governing the ethical use of pre-existing genetic datasets. The harmonization of these diverse data sources enabled us to conduct the most comprehensive MR analysis to date on the potential causal

relationships between AIT and cancer susceptibility across multiple organ systems.

2.3. Genome-wide association study-based IV selection

Our MR analysis strictly adhered to the three fundamental IV assumptions to ensure valid causal inference. First, we confirmed a robust genetic association between the selected IVs and AIT/HT, establishing a strong exposure–instrument relationship. Second, we rigorously verified that the genetic variants operated exclusively through the hypothesized biological pathway, with no pleiotropic effects mediated by confounding factors. Third, we ensured the selected IVs influenced cancer risk solely through their association with AIT/HT, without alternative causal pathways. For instrument selection, we implemented a multi-stage filtering process incorporating state-of-the-art methodological standards: (i) single-nucleotide polymorphisms (SNPs) associated with the exposure at a locus-wide significance threshold ($p<1\times10^{-5}$) were retained as potential IVs. This threshold balanced the need for a sufficient number of IVs while maintaining biological relevance. (ii) European ancestry samples from the 1,000 Genomes Project Phase 3 were employed as the reference panel for estimating linkage disequilibrium (LD).[21] Variant clumping was performed using the following parameters: a pairwise LD threshold $R^2 < 0.001$ and a physical distance window of 10,000 kb. This process retained only the most statistically significant SNP (i.e., the one with the lowest *p*-value) from each LD block, effectively eliminating correlated variants that could bias results. (iii) Instrument strength was quantified using the formula:

$$F = [(N–K–1)/K]\times[R^2/(1–R^2)] \quad (I)$$

where N = sample size, K = number of instruments, and R^2 = the proportion of exposure variance explained by the SNPs.

We applied a conservative threshold ($F \geq 10$) to minimize weak instrument bias, excluding all variants below this cutoff.[22] Thus, weaker instruments were excluded to prevent potential attenuation of causal estimates. (iv) SNPs associated with possible confounders identified in prior studies (e.g., cancers and diabetes mellitus)[23,24] were excluded. This exclusion was validated using the NHGRI-EBI GWAS Catalog (www.ebi.ac.uk/gwas),[25] which confirmed that the selected SNPs were not linked to any known confounders, thereby reinforcing the validity of the IVs. This step was crucial for maintaining the exclusion restriction assumption.

2.4. MR analysis

All statistical analyses were performed using R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria), with the TwoSampleMR package (version 0.5.7) as our primary analytical framework. We implemented a comprehensive, multi-method approach for reciprocal two-sample MR analysis to assess the bidirectional relationships between AIT/HT and cancer risk. The workflow began with meticulous data harmonization to ensure allele alignment and strand consistency across all exposure and outcome datasets, excluding palindromic SNPs with intermediate allele frequencies to avoid potential bias from ambiguous strand orientation. For our primary analysis, we applied inverse-variance weighted (IVW) meta-analysis, which combines SNP-specific Wald ratio estimates using random-effects models.[26] We selected IVW because of its optimal statistical properties: (i) providing minimum-variance unbiased estimates under valid instrument assumptions; (ii) enhancing statistical efficiency through optimal weighting; and (iii) yielding consistent causal effects when the no horizontal pleiotropy assumption holds.[27] To validate our findings and assess potential violations of MR assumptions, we supplemented the IVW analysis with four additional MR methods. The MR-Egger method, a commonly used approach in MR studies, applies linear regression to evaluate the causal effect of an exposure on an outcome while simultaneously estimating and adjusting for potential directional pleiotropy through Egger regression, thereby improving the precision of causal effect estimates.[28] The weighted median method serves as a robust approach to address potential bias from invalid instruments, enhancing the reliability of MR findings.[29] The simple mode and weighted mode methods function as randomization techniques that mitigate confounding effects through instrument grouping, thereby reinforcing the robustness of the results.[30] Using the same analytical procedures, we performed reverse MR analysis, treating malignancies as the exposure and AIT/HT as the outcome. To facilitate clinical interpretation, log-odds estimates from GWAS summary statistics were transformed into odds ratios (ORs) and corresponding 95% confidence intervals (95% CIs) using exponential transformation. Statistical significance was defined as $p<0.05$. Notably, we maintained a conservative approach to missing data by excluding, rather than imputing, incomplete observations, thereby preserving the integrity of our analytical dataset.

2.5. Quality control

To thoroughly assess the validity of our MR assumptions and the robustness of our findings, we implemented a comprehensive suite of sensitivity analyses. Instrument heterogeneity was evaluated using Cochran's *Q* test within the IVW framework, a commonly used statistical method for assessing heterogeneity among IVs in MR studies.[31] The resulting *p*-value from this test plays a crucial role

in determining whether significant heterogeneity exists across the selected IVs. Statistical significance ($p < 0.05$) indicates likely heterogeneity among the IVs. Horizontal pleiotropy was examined using the MR-Egger intercept test. A significant MR-Egger intercept suggests directional horizontal pleiotropy.[28] Furthermore, we applied the MR-Pleiotropy RESidual Sum and Outlier (PRESSO) method to detect and remove genetic variants exhibiting horizontal pleiotropy, thereby minimizing potential bias in our causal effect estimates.[32] To visually evaluate result robustness, we generated both scatter plots and funnel plots. Scatter plots displayed SNP-specific Wald ratios to visually inspect for outliers and assess the overall consistency of effect directions. Funnel plots provided additional evaluation of effect size symmetry, where asymmetry could indicate potential pleiotropy or other biases. In addition, leave-one-out analysis tested whether MR estimates were driven by individual SNPs. This method systematically excluded each SNP in turn, evaluating whether any single variant disproportionately influenced the causal effect estimates, thus confirming the stability and robustness of our findings. All sensitivity analyses were conducted using the latest versions of specialized R packages (TwoSampleMR and MR-PRESSO) with consistent application across all exposure–outcome pairs. Through this comprehensive approach—combining statistical tests, outlier detection methods, and visual diagnostics—we obtained multiple lines of evidence supporting the validity of our causal inferences and the appropriateness of our IV assumptions.

3. Results

3.1. Genetic liability to AIT/HT and risk of thyroid cancers

Through rigorous instrument selection, we identified 15 high-quality SNPs from the FinnGen dataset (finngen_R12_E4_THYROIDITAUTOIM) and 70 SNPs from the IEU OpenGWAS dataset (ebi-a-GCST90018855) as genetic instruments for AIT/HT. These instruments demonstrated strong associations with AIT/HT (all F-statistics > 10) while meeting all assumptions for valid IVs. For outcome assessment, we incorporated six independent GWAS datasets representing malignant thyroid neoplasms, along with three subtype-specific datasets (PTC, follicular thyroid adenocarcinoma, and medullary thyroid carcinoma) and one benign thyroid neoplasm dataset (detailed in Table 1). Using MR-IVW analysis, we estimated the OR for AIT/HT per log-odds increase in genetic liability to each outcome (Figure 2). The number of SNPs varied across analyses due to either unavailability in outcome studies or inability to harmonize between datasets caused by coding-strand ambiguities. Our IVW analysis revealed no statistically significant associations between genetically predicted AIT/HT and any form of thyroid cancer (Figure 2). The ORs per log-odds increase in genetic liability ranged from 0.873 to 1.064 across all thyroid neoplasm outcomes, with all 95% CIs encompassing the null value of 1.0 (Figure 2). For analyses using the FinnGen AIT dataset, extensive sensitivity analyses consistently supported the robustness of these null findings: (i) no significant heterogeneity (assessed by Cochran's Q test), (ii) no evidence of horizontal pleiotropy (assessed by the MR-Egger intercept test), and (iii) no outlier variants (assessed by the MR-PRESSO global test), supporting the robustness of our null findings (Tables S1 and S2). However, analyses incorporating the HT dataset (ebi-a-GCST90018855) revealed potential methodological complexities: (i) indicative horizontal pleiotropy and heterogeneity in analyses with the FinnGen R12 malignant thyroid neoplasms data and the EBI-a-GCST90018929 thyroid cancer data; and (ii) potential horizontal pleiotropy in the analysis with the FinnGen R12 follicular thyroid adenocarcinoma dataset (Tables S3 and S4). In summary, our comprehensive MR analysis found no significant causal relationship between genetic predisposition to AIT/HT and thyroid malignancy risk.

3.2. Causal relationships between AIT/HT and extra-thyroidal cancer risks

We further investigated possible causal relationships between AIT/HT and 33 extra-thyroidal cancers (Table 1). Using IVW analysis, causal associations were observed between AIT and the incidence of malignant neoplasm of testis (OR = 1.159, 95% CI = 1.031–1.304, p=0.014), non-Hodgkin lymphoma (NHL; OR = 1.099, 95% CI = 1.049–1.150, p<0.001), and primary lymphoid and hematopoietic malignant neoplasms (OR = 1.050, 95% CI = 1.008–1.094, p=0.020) (Figure 3), whereas HT was associated with an increased risk of malignant neoplasm of the brain (OR = 1.108, 95% CI = 1.033–1.189, p=0.004) (Figure 3). These findings were robust across all four complementary MR methods (weighted median, MR-Egger, simple mode, and weighted mode), as detailed in Table S5. The genome-wide significant SNPs driving these associations and their characteristics are comprehensively documented in Table S6. However, sensitivity analyses indicated the presence of horizontal pleiotropy and heterogeneity in the IV estimates for AIT in relation to primary lymphoid and hematopoietic malignant neoplasms (Tables S1 and S2). To reinforce the credibility of other indicated causal associations, we implemented additional sensitivity analyses (scatter plots, funnel plots, and leave-one-out forest plots) within the identified causal relationships, confirming that the estimated effects were unlikely to be

Exposure	Outcome	nsnp	Method	pval	OR (95% CI)
Autoimmune thyroiditis	Benign neoplasm of thyroid (FinnGen R12)	14	Inverse-variance weighted	0.591	0.976 (0.893 to 1.067)
Autoimmune thyroiditis	Malignant neoplasm of thyroid (FinnGen R12)	14	Inverse-variance weighted	0.823	1.007 (0.950 to 1.066)
Autoimmune thyroiditis	Papillary adenocarcinoma of thyroid (FinnGen R12)	14	Inverse-variance weighted	0.961	1.002 (0.941 to 1.067)
Autoimmune thyroiditis	Follicular adenocarcinoma of thyroid (FinnGen R12)	14	Inverse-variance weighted	0.748	0.973 (0.826 to 1.147)
Autoimmune thyroiditis	Medullary carcinoma of thyroid (FinnGen R12)	14	Inverse-variance weighted	0.764	0.939 (0.620 to 1.420)
Autoimmune thyroiditis	Thyroid cancer (ebi-a-GCST90018929)	13	Inverse-variance weighted	0.835	1.010 (0.916 to 1.115)
Autoimmune thyroiditis	Thyroid cancer (ebi-a-GCST90013863)	10	Inverse-variance weighted	0.094	0.873 (0.744 to 1.023)
Autoimmune thyroiditis	Thyroid cancer (ebi-a-GCST90013867)	10	Inverse-variance weighted	0.094	0.873 (0.744 to 1.023)
Autoimmune thyroiditis	Malignant neoplasm of thyroid (UK Biobank C3)	10	Inverse-variance weighted	0.177	1.000 (1.000 to 1.000)
Hashimoto's thyroiditis	Benign neoplasm of thyroid (FinnGen R12)	61	Inverse-variance weighted	0.508	0.971 (0.888 to 1.061)
Hashimoto's thyroiditis	Malignant neoplasm of thyroid (FinnGen R12)	61	Inverse-variance weighted	0.757	1.011 (0.945 to 1.081)
Hashimoto's thyroiditis	Papillary adenocarcinoma of thyroid (FinnGen R12)	61	Inverse-variance weighted	0.824	1.008 (0.942 to 1.078)
Hashimoto's thyroiditis	Follicular adenocarcinoma of thyroid (FinnGen R12)	61	Inverse-variance weighted	0.397	0.924 (0.770 to 1.109)
Hashimoto's thyroiditis	Medullary carcinoma of thyroid (FinnGen R12)	61	Inverse-variance weighted	0.752	1.064 (0.724 to 1.563)
Hashimoto's thyroiditis	Thyroid cancer (ebi-a-GCST90018929)	69	Inverse-variance weighted	0.277	1.060 (0.954 to 1.179)
Hashimoto's thyroiditis	Thyroid cancer (ebi-a-GCST90013863)	60	Inverse-variance weighted	0.701	0.979 (0.876 to 1.093)
Hashimoto's thyroiditis	Thyroid cancer (ebi-a-GCST90013867)	60	Inverse-variance weighted	0.691	0.977 (0.874 to 1.094)
Hashimoto's thyroiditis	Thyroid cancer (ieu-a-1082)	9	Inverse-variance weighted	0.942	0.973 (0.469 to 2.019)
Hashimoto's thyroiditis	Malignant neoplasm of thyroid (UK Biobank C3)	58	Inverse-variance weighted	0.344	1.000 (1.000 to 1.000)

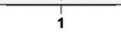

Figure 2. Forest plot showing the effects of autoimmune thyroiditis/Hashimoto's thyroiditis on the risk of thyroid neoplasms using the inverse-variance weighted method
Abbreviations: CI: Confidence interval; nsnp: number of SNPs; OR: Odds ratio; pval: *p*-value; UK: United Kingdom.

Exposure	Outcome	nsnp	Method	pval	OR (95% CI)
Autoimmune thyroiditis	Malignant neoplasm of testis	14	MR-Egger	0.457	1.133 (0.823 to 1.560)
		14	Weighted median	**0.014**	1.209 (1.039 to 1.407)
		14	Inverse-variance weighted	**0.014**	1.159 (1.031 to 1.304)
		14	Simple mode	0.241	1.173 (0.909 to 1.514)
		14	Weighted mode	0.106	1.216 (0.975 to 1.515)
Autoimmune thyroiditis	Non-Hodgkin lymphoma	14	MR-Egger	**0.021**	1.181 (1.044 to 1.336)
		14	Weighted median	**0.011**	1.087 (1.019 to 1.160)
		14	Inverse-variance weighted	**<0.001**	1.099 (1.049 to 1.150)
		14	Simple mode	0.698	1.028 (0.897 to 1.178)
		14	Weighted mode	0.781	1.023 (0.876 to 1.194)
Autoimmune thyroiditis	Primary lymphoid and hematopoietic malignant neoplasms	14	MR-Egger	0.163	1.090 (0.973 to 1.221)
		14	Weighted median	**0.015**	1.061 (1.011 to 1.113)
		14	Inverse-variance weighted	**0.020**	1.050 (1.008 to 1.094)
		14	Simple mode	0.523	1.029 (0.945 to 1.120)
		14	Weighted mode	0.177	1.056 (0.980 to 1.138)
Hashimoto's thyroiditis	Malignant neoplasm of brain	61	MR-Egger	0.121	1.084 (0.980 to 1.199)
		61	Weighted median	0.221	1.083 (0.953 to 1.231)
		61	Inverse-variance weighted	**0.004**	1.108 (1.033 to 1.189)
		61	Simple mode	0.885	1.019 (0.795 to 1.305)
		61	Weighted mode	0.085	1.099 (0.989 to 1.222)

Figure 3. Forest plot illustrating the effects of autoimmune thyroiditis/Hashimoto's thyroiditis on the risk of malignant neoplasm of the testis, non-Hodgkin lymphoma, primary lymphoid and hematopoietic malignant neoplasms, and malignant neoplasm of the brain, using multiple Mendelian randomization methods
Abbreviations: CI: Confidence interval; nsnp: number of SNPs; OR: Odds ratio; pval: *p*-value.

driven by any single genetic instrument (Figures S1-S3). Reverse MR analysis further excluded mutual associations as a potential explanation for the observed relationships between AIT/HT and the identified cancers (Figure 4).

AIT/HT showed no significant genetic correlation with other extra-thyroidal cancer types, such as bone cancer, breast cancer, lung cancer, digestive system cancers, or skin cancers (Figures 5 and 6). Nevertheless, our sensitivity analyses identified potential horizontal pleiotropy and heterogeneity in several cancer-specific analyses. For AIT, these methodological concerns were particularly notable for malignancies of the anus/anal canal, bronchus/lung (especially non-small-cell lung cancer), cervix uteri, colorectum (both adenocarcinoma and general colorectal cancer), rectum, and skin (Tables S1 and S2). Similarly, HT analyses showed comparable issues for cancers of the adrenal gland, breast, prostate, colorectum, and skin, as well as for malignant melanoma, primary lymphoid/hematopoietic neoplasms, and NHL (Tables S3 and S4). These findings highlight the importance of careful interpretation of MR results in the context of potential pleiotropic effects, particularly for cancers where shared biological pathways with autoimmunity may exist.

Exposure	Outcome	nsnp	Method	pval	OR (95% CI)
Non−Hodgkin lymphoma	Autoimmune thyroidis	47	Inverse−variance weighted	0.536	0.939 (0.769 to 1.146)
Primary lymphoid and hematopoietic malignant neoplasms	Autoimmune thyroidis	43	Inverse−variance weighted	0.060	0.775 (0.594 to 1.011)
Malignant neoplasm of testis	Autoimmune thyroidis	15	Inverse−variance weighted	0.261	0.934 (0.830 to 1.052)
Malignant neoplasm of brain	Hashimoto's thyroidis	14	Inverse−variance weighted	0.994	1.000 (0.950 to 1.052)

Figure 4. Forest plot depicting the reverse effects of malignant neoplasm of the testis, non-Hodgkin lymphoma, primary lymphoid and hematopoietic malignant neoplasms, and malignant neoplasm of the brain on the risk of autoimmune thyroiditis/Hashimoto's thyroiditis
Abbreviations: CI: Confidence interval; nsnp: number of SNPs; OR: Odds ratio; pval: *p*-value.

Exposure	Outcome	nsnp	Method	pval	OR (95% CI)
Autoimmune thyroiditis	Malignant neoplasm of adrenal gland	14	Inverse−variance weighted	0.767	0.971 (0.797 to 1.182)
Autoimmune thyroiditis	Malignant neoplasm of anus and anal canal	14	Inverse−variance weighted	0.650	1.050 (0.852 to 1.293)
Autoimmune thyroiditis	Malignant neoplasm of brain	14	Inverse−variance weighted	0.727	1.013 (0.944 to 1.087)
Autoimmune thyroiditis	Malignant neoplasm of head and neck	14	Inverse−variance weighted	0.880	0.996 (0.940 to 1.055)
Autoimmune thyroiditis	Malignant neoplasm of oral cavity	14	Inverse−variance weighted	0.651	0.982 (0.910 to 1.061)
Autoimmune thyroiditis	Malignant neoplasm of bone and articular cartilage	14	Inverse−variance weighted	0.310	0.932 (0.813 to 1.068)
Autoimmune thyroiditis	Malignant neoplasm of breast, ER−negative	14	Inverse−variance weighted	0.618	0.992 (0.960 to 1.025)
Autoimmune thyroiditis	Malignant neoplasm of breast, ER−positive	14	Inverse−variance weighted	0.181	1.019 (0.991 to 1.047)
Autoimmune thyroiditis	Malignant neoplasm of breast	14	Inverse−variance weighted	0.684	1.005 (0.982 to 1.028)
Autoimmune thyroiditis	Malignant neoplasm of bronchus and lung	14	Inverse−variance weighted	0.263	1.033 (0.976 to 1.093)
Autoimmune thyroiditis	Non−small cell lung cancer	14	Inverse−variance weighted	0.105	1.048 (0.990 to 1.109)
Autoimmune thyroiditis	Malignant neoplasm of urinary organs	14	Inverse−variance weighted	0.326	0.976 (0.929 to 1.025)
Autoimmune thyroiditis	Malignant neoplasm of bladder	14	Inverse−variance weighted	0.871	0.996 (0.952 to 1.043)
Autoimmune thyroiditis	Malignant neoplasm of kidney	14	Inverse−variance weighted	0.502	0.983 (0.936 to 1.033)
Autoimmune thyroiditis	Malignant neoplasm of cervix uteri	14	Inverse−variance weighted	0.753	0.977 (0.846 to 1.128)
Autoimmune thyroiditis	Malignant neoplasm of corpus uteri	14	Inverse−variance weighted	0.970	0.999 (0.947 to 1.054)
Autoimmune thyroiditis	Malignant neoplasm of ovary	14	Inverse−variance weighted	0.359	1.032 (0.965 to 1.103)
Autoimmune thyroiditis	Malignant neoplasm of prostate	14	Inverse−variance weighted	0.115	0.978 (0.951 to 1.005)
Autoimmune thyroiditis	Malignant neoplasm of stomach	14	Inverse−variance weighted	0.337	1.035 (0.965 to 1.110)
Autoimmune thyroiditis	Malignant neoplasm of intrahepatic ducts, biliary tract and gallbladder	14	Inverse−variance weighted	0.511	1.022 (0.958 to 1.090)
Autoimmune thyroiditis	Malignant neoplasm of pancreas	14	Inverse−variance weighted	0.782	1.009 (0.949 to 1.072)
Autoimmune thyroiditis	Colon adenocarcinoma	14	Inverse−variance weighted	0.972	0.999 (0.953 to 1.047)
Autoimmune thyroiditis	Malignant neoplasm of colon	14	Inverse−variance weighted	0.807	0.996 (0.960 to 1.032)
Autoimmune thyroiditis	Colorectal adenocarcinoma	14	Inverse−variance weighted	0.481	1.018 (0.968 to 1.071)
Autoimmune thyroiditis	Colorectal cancer	14	Inverse−variance weighted	0.441	1.017 (0.975 to 1.060)
Autoimmune thyroiditis	Malignant neoplasm of small intestine	14	Inverse−variance weighted	0.465	1.036 (0.942 to 1.141)
Autoimmune thyroiditis	Malignant neoplasm of rectum	14	Inverse−variance weighted	0.187	1.049 (0.977 to 1.125)
Autoimmune thyroiditis	Malignant neoplasm of skin	14	Inverse−variance weighted	0.877	0.998 (0.974 to 1.023)
Autoimmune thyroiditis	Malignant melanoma	14	Inverse−variance weighted	0.079	0.966 (0.929 to 1.004)
Autoimmune thyroiditis	Chronic lymphocytic leukaemia and small lyphocytis leukaemia	14	Inverse−variance weighted	0.873	1.009 (0.909 to 1.119)

Figure 5. Forest plot showing the effects of autoimmune thyroiditis on the risk of pan-cancer
Abbreviations: CI: Confidence interval; ER: Estrogen receptor; nsnp: number of SNPs; OR: Odds ratio; pval: *p*-value.

4. Discussion

In this large-scale MR study, we systematically investigated potential causal relationships between genetic predisposition to AIT/HT and cancer susceptibility across 37 distinct malignancies, including thyroid neoplasms (analyzed both collectively and by major histological subtypes) and 33 extra-thyroidal cancers. Our comprehensive analysis yielded several important findings. First, we found no evidence supporting a causal role of AIT/HT in the development of thyroid cancers, including papillary, follicular, and medullary subtypes, a null association that remained robust across multiple sensitivity analyses and alternative MR methods. Second, we identified significant positive associations between AIT/HT and specific extra-thyroidal malignancies, with AIT showing causal links to testicular cancer (OR = 1.099), NHL (OR=1.099), and primary lymphoid/hematopoietic malignancies (OR = 1.050), whereas HT was associated with brain malignancies (OR = 1.108). These findings provide novel insights into the complex interplay between thyroid autoimmunity and oncogenesis, suggesting that although AIT/HT may not influence thyroid carcinogenesis, it could contribute to cancer risk at certain extra-thyroidal sites through shared immunological pathways or systemic inflammatory effects.

Our MR analysis provides compelling genetic evidence that AIT/HT does not directly contribute to the development of thyroid neoplasms. The comprehensive assessment of benign thyroid neoplasm, thyroid cancer as a single analytical entity, and all major histological subtypes of thyroid cancer (papillary, follicular, and medullary carcinomas) consistently yielded null associations, with CIs spanning the null value across all analyses. Our results corroborate earlier studies that challenge the direct involvement of thyroid autoimmunity in thyroid carcinogenesis.[24,33] The apparent clinical co-occurrence

Exposure	Outcome	nsnp	Method	pval	OR (95% CI)
Hashimoto's thyroiditis	Malignant neoplasm of adrenal gland	61	Inverse−variance weighted	0.688	0.954 (0.760 to 1.199)
Hashimoto's thyroiditis	Malignant neoplasm of anus and anal canal	61	Inverse−variance weighted	0.817	1.020 (0.859 to 1.212)
Hashimoto's thyroiditis	Malignant neoplasm of head and neck	61	Inverse−variance weighted	0.126	1.041 (0.989 to 1.095)
Hashimoto's thyroiditis	Malignant neoplasm of oral cavity	61	Inverse−variance weighted	0.252	1.045 (0.969 to 1.128)
Hashimoto's thyroiditis	Malignant neoplasm of bone and articular cartilage	61	Inverse−variance weighted	0.476	1.047 (0.922 to 1.190)
Hashimoto's thyroiditis	Malignant neoplasm of breast, ER−negative	61	Inverse−variance weighted	0.551	1.010 (0.977 to 1.045)
Hashimoto's thyroiditis	Malignant neoplasm of breast, ER−positive	61	Inverse−variance weighted	0.948	0.999 (0.969 to 1.029)
Hashimoto's thyroiditis	Malignant neoplasm of breast	61	Inverse−variance weighted	0.838	1.003 (0.978 to 1.028)
Hashimoto's thyroiditis	Malignant neoplasm of bronchus and lung	61	Inverse−variance weighted	0.917	1.002 (0.967 to 1.038)
Hashimoto's thyroiditis	Non−small cell lung cancer	61	Inverse−variance weighted	0.568	0.988 (0.946 to 1.031)
Hashimoto's thyroiditis	Malignant neoplasm of urinary organs	61	Inverse−variance weighted	0.792	0.993 (0.944 to 1.045)
Hashimoto's thyroiditis	Malignant neoplasm of bladder	61	Inverse−variance weighted	0.869	0.996 (0.951 to 1.043)
Hashimoto's thyroiditis	Malignant neoplasm of kidney	61	Inverse−variance weighted	0.686	0.989 (0.938 to 1.043)
Hashimoto's thyroiditis	Malignant neoplasm of cervix uteri	61	Inverse−variance weighted	0.577	1.031 (0.927 to 1.146)
Hashimoto's thyroiditis	Malignant neoplasm of corpus uteri	61	Inverse−variance weighted	0.122	0.953 (0.896 to 1.013)
Hashimoto's thyroiditis	Malignant neoplasm of ovary	61	Inverse−variance weighted	0.951	0.998 (0.937 to 1.063)
Hashimoto's thyroiditis	Malignant neoplasm of prostate	61	Inverse−variance weighted	0.366	0.982 (0.946 to 1.021)
Hashimoto's thyroiditis	Malignant neoplasm of testis	61	Inverse−variance weighted	0.129	0.914 (0.813 to 1.026)
Hashimoto's thyroiditis	Malignant neoplasm of stomach	61	Inverse−variance weighted	0.697	1.014 (0.947 to 1.084)
Hashimoto's thyroiditis	Malignant neoplasm of intrahepatic ducts, biliary tract and gallbladder	61	Inverse−variance weighted	0.861	1.006 (0.943 to 1.072)
Hashimoto's thyroiditis	Malignant neoplasm of pancreas	61	Inverse−variance weighted	0.831	1.006 (0.950 to 1.067)
Hashimoto's thyroiditis	Colon adenocarcinoma	61	Inverse−variance weighted	0.325	1.025 (0.976 to 1.075)
Hashimoto's thyroiditis	Malignant neoplasm of colon	61	Inverse−variance weighted	0.899	1.003 (0.961 to 1.047)
Hashimoto's thyroiditis	Colorectal adenocarcinoma	61	Inverse−variance weighted	0.461	1.015 (0.976 to 1.055)
Hashimoto's thyroiditis	Colorectal cancer	61	Inverse−variance weighted	0.617	1.009 (0.973 to 1.047)
Hashimoto's thyroiditis	Malignant neoplasm of small intestine	61	Inverse−variance weighted	0.838	1.011 (0.907 to 1.127)
Hashimoto's thyroiditis	Malignant neoplasm of rectum	61	Inverse−variance weighted	0.301	1.025 (0.978 to 1.075)
Hashimoto's thyroiditis	Malignant neoplasm of skin	61	Inverse−variance weighted	0.351	0.982 (0.945 to 1.020)
Hashimoto's thyroiditis	Malignant melanoma	61	Inverse−variance weighted	0.562	0.986 (0.942 to 1.033)
Hashimoto's thyroiditis	Chronic lymphocytic leukaemia and small lyphocytis leukaemia	61	Inverse−variance weighted	0.421	1.048 (0.935 to 1.174)
Hashimoto's thyroiditis	Primary lymphoid and hematopoietic malignant neoplasms	61	Inverse−variance weighted	0.555	1.012 (0.972 to 1.055)
Hashimoto's thyroiditis	Non−Hodgkin lymphoma	61	Inverse−variance weighted	0.592	1.015 (0.961 to 1.072)

Figure 6. Forest plot illustrating the effects of Hashimoto's thyroiditis on the risk of pan-cancer
Abbreviations: CI: Confidence interval; ER: Estrogen receptor; nsnp: number of SNPs; OR: Odds ratio; pval: *p*-value.

of AIT and PTC, reported in 8–36.4% of cases in observational studies,[34] may instead reflect diagnostic detection bias, shared risk factors, or tumor-induced immune responses, rather than a causal relationship. This interpretation is supported by the paradoxical observation that PTC patients with concurrent AIT often demonstrate better prognostic outcomes, including lower rates of extrathyroidal extension, lymph node metastasis, and advanced tumor-node-metastasis staging features,[35-37] suggesting that AIT may represent a protective host immune response rather than a tumor-promoting factor. The potential mechanisms linking thyroid autoimmunity to carcinogenesis are complex and likely involve dual biological processes. On one hand, chronic thyroid inflammation could theoretically promote malignant transformation through reactive oxygen species-mediated DNA damage and sustained proliferative signaling within the inflammatory microenvironment.[38] Concurrently, compensatory thyroid-stimulating hormone elevation, frequently observed in AIT/HT patients, may further drive PTC risk, even at subclinical levels.[39] However, our genetic analysis suggests that these mechanisms, while biologically plausible, do not appear to be directly mediated by the genetic variants associated with AIT/HT susceptibility. This conclusion is further supported by prior MR studies that systematically evaluated various thyroid cancer risk factors, including inflammatory markers and thyroid function parameters, and similarly found no significant causal associations.[23] These negative results[23,24] provide independent validation of our study. The robustness of our null findings is strengthened by several methodological considerations. Our sensitivity analyses revealed minimal evidence of significant heterogeneity or horizontal pleiotropy in the AIT genetic instruments, suggesting that the null associations were not substantially influenced by these potential biases. However, we did identify some evidence of potential pleiotropic effects in the HT-specific analyses for malignant thyroid neoplasms and follicular carcinoma, indicating that these particular associations should be interpreted with caution and may warrant further investigation. These findings collectively suggest that, while thyroid autoimmunity and thyroid cancer may frequently coexist clinically, this association likely reflects shared underlying susceptibility factors or secondary phenomena, rather than a direct causal relationship.

Beyond thyroid cancers, we systematically evaluated the causal relationship between AIT/HT and various malignancies, revealing distinct patterns of association. We found that AIT was associated with an increased risk of NHL, primary lymphoid and hematopoietic malignancies, and malignant neoplasms of the testis. These findings are particularly compelling in the context

of thyroid lymphomagenesis, where chronic inflammation in AIT may drive B-cell proliferation, as evidenced by the well-documented increased risk of primary thyroid lymphoma (predominantly the diffuse large B-cell lymphoma subtype) in AIT patients.[11,40-42] Lymphomas comprise B-cell and T-cell malignancies arising from the lymphoid lineage, classified based on cellular origin and differentiation stage. Primary thyroid lymphoma, a less common form of thyroid cancer, is a subtype of NHL that originates in the thyroid, with diffuse large B-cell lymphoma being the predominant histological subtype.[43] Research has established a strong association between AIT and thyroid lymphoma: patients with AIT exhibit a significantly elevated risk of developing PTL compared to the general population.[44-46] Genetic studies have further explored shared susceptibility loci between NHL and autoimmune disorders (e.g., type 1 diabetes, Crohn's disease, and rheumatoid arthritis). Notably, two distinct regions within the major histocompatibility complex (MHC) have been identified as key overlapping risk loci.[47] In our study, among 14 SNPs linked to both AIT and NHL, three were located within the MHC region (Chr6: 26–34 Mb). Importantly, even after excluding these MHC-associated SNPs, MR-IVW analysis continued to indicate AIT as a risk factor for NHL development (OR = 1.060, 95% CI = 1.003–1.120, p=0.036; Table S7), suggesting the contribution of additional genetic mechanisms outside the MHC. The observed association between AIT and NHL may stem from shared immunological pathways, such as abnormal B-cell activation or persistent antigen stimulation.[48] Given that thyroid lymphoma is highly treatable when diagnosed early, identifying risk factors (including genetic predispositions) is critical for timely diagnosis and intervention.

Beyond NHL associations, AIT was also genetically linked to primary lymphoid and hematopoietic malignancies. However, sensitivity analyses indicated potential heterogeneity and horizontal pleiotropy in these analyses, warranting cautious interpretation. Notably, our study identified AIT as a novel genetic risk factor for testicular cancer, providing clarity to previous inconsistencies in the literature regarding this potential association. While some epidemiological studies have suggested a possible link between thyroid autoimmunity and testicular malignancies, the evidence has been limited and conflicting.[11] As one of the first large-scale data-mining investigations, our work helps address the critical gap in the causal association between AIT and testicular cancer, warranting further mechanistic exploration. The biological plausibility of this relationship may involve shared autoimmune pathways or hormonal interactions, though the exact mechanisms remain to be elucidated through future experimental and clinical studies. Separately, using the HT dataset, we identified a previously undocumented causal association with brain cancer. This novel finding positions thyroid autoimmunity as a potential modulator of central nervous system (CNS) tumorigenesis, possibly through mechanisms involving neuroinflammatory pathways or blood–brain barrier disruption. The immunological cross-talk between the thyroid and CNS merits particular attention in future research, especially given the increasing recognition of neuroinflammation's role in various brain pathologies. It is noteworthy that our analyses revealed no overlapping cancer associations between the AIT and HT datasets. This divergence could reflect either: (i) a true absence of broad associations between thyroid autoimmunity and pan-cancer risk; or (ii) methodological limitations stemming from dataset heterogeneity, including differences in case definitions, diagnostic criteria, and population characteristics between the AIT and HT cohorts. The latter possibility highlights a critical challenge in MR research—the lack of standardized diagnostic classifications across studies. This underscores the urgent need for future large-scale, harmonized cohorts that combine detailed clinical phenotyping with comprehensive genetic data, using unified AIT/HT diagnostic criteria to enable more robust conclusions about cancer risk in autoimmune thyroid disorders. Such efforts will be essential for clarifying whether the observed associations represent true biological relationships or methodological artifacts, and for identifying high-risk subgroups that might benefit from targeted cancer surveillance strategies.

Our large-scale MR analysis revealed no statistically significant evidence of a causal relationship between AIT/HT and multiple major cancer types, including malignancies of the bone, breast, lung, digestive system, and skin. These null associations persisted across multiple MR methods, demonstrating robustness against potential violations of MR assumptions. However, we observed notable heterogeneity and indications of horizontal pleiotropy in the analyses for certain cancers, particularly anal, lung (including non-small-cell carcinoma), cervical, colorectal, and skin cancers. These findings suggest that unmeasured confounding, shared genetic pathways, or bidirectional effects may influence these associations, thereby complicating causal inference. The absence of significant MR associations does not definitively rule out a biological link between AIT/HT and cancer risk, as potential limitations (e.g., weak instrument bias, tissue-specific effects of thyroid autoimmunity, or latency in cancer development) could obscure true causal relationships. Moreover, the observed pleiotropy highlights the complexity of disentangling AIT–cancer

interactions, which may involve immune dysregulation, hormonal influences, or treatment-related modifications of risk. Thus, while our study does not support a broad causal role of AIT/HT in most major cancers, the presence of heterogeneity and pleiotropy in certain malignancies necessitates cautious interpretation. Future research integrating longitudinal clinical data, tissue-specific molecular profiling, and more refined genetic instruments may help clarify these nuanced relationships.

Our findings significantly reshape the current understanding of AIT's role in cancer development, with important clinical and research implications. Contrary to conventional assumptions, we found no causal association between AIT and thyroid cancers, thereby challenging the long-held view of thyroid autoimmunity as a direct driver of thyroid carcinogenesis. This revelation suggests that previously observed epidemiological links may instead reflect confounding by shared environmental exposures (e.g., iodine status, radiation) or lifestyle factors common to both conditions. These insights should prompt a re-evaluation of clinical practice guidelines. Rather than recommending intensive thyroid cancer screening for all AIT patients based solely on their autoimmune status, public health resources would be better allocated toward addressing the more clinically urgent challenge of AIT potentially masking thyroid malignancies. This is particularly relevant given the well-documented limitations in current diagnostic protocols, where chronic inflammation and structural changes in AIT can obscure malignant features on ultrasound and fine-needle aspiration.[34] The robust associations we identified between AIT/HT and specific extra-thyroidal malignancies, particularly NHL and brain cancers, open new avenues for mechanistic research into immune-mediated oncogenesis. These relationships likely involve complex immunological pathways that warrant systematic investigation, including: (i) chronic B-cell activation and proliferation in NHL pathogenesis, potentially mediated through thyroid antigen-driven stimulation; (ii) neuroimmune cross-talk in brain cancer development, possibly involving thyroid hormone-mediated modulation of glial cell function or blood–brain barrier integrity; and (iii) shared immune checkpoint dysregulation across both autoimmune and neoplastic processes. Future research should adopt a multi-dimensional approach to unravel these mechanisms, incorporating deep immunophenotyping, system biology approaches, experimental models, and clinical-translational studies. In addition, integrating multi-omics data, such as transcriptomics and epigenomics, could provide deeper insights into the biological processes linking AIT to cancer. These investigations should be prioritized given their potential to reveal novel therapeutic targets at the intersection of autoimmunity and cancer biology, while also informing more personalized surveillance strategies for AIT patients based on their individual risk profiles. The development of biomarkers integrating genetic susceptibility, immune signatures, and clinical parameters could ultimately enable risk-stratified approaches to cancer screening.

The present study possesses several notable strengths that enhance the validity and impact of its findings. Our analysis leveraged large-scale, well-powered GWAS datasets encompassing hundreds of thousands of individuals, providing substantial statistical power to detect even modest genetic associations. We employed rigorous MR methodologies, including multiple complementary approaches, to ensure robust causal inference. The comprehensive sensitivity analyses we conducted, which assessed and adjusted for potential pleiotropy, heterogeneity, and other biases, further strengthen the reliability of our conclusions. In addition, our systematic evaluation across multiple cancer types represents one of the most extensive investigations of AIT-cancer relationships to date. However, several important methodological limitations warrant consideration when interpreting these results. First, the predominantly European ancestry of our GWAS sources limits the generalizability of our findings to other ethnic populations. Given known variations in allele frequencies, genetic architecture, and population-specific environmental exposures across ethnic groups, our results may not fully translate to non-European populations. For instance, the prevalence and clinical manifestations of AIT/HT differ substantially between Asian and European populations, potentially affecting cancer risk associations. Second, while MR provides powerful causal inference capabilities, its validity hinges on three critical assumptions, particularly the absence of horizontal pleiotropy. Although we implemented state-of-the-art sensitivity analyses to detect and adjust for pleiotropic effects, complete elimination of this potential bias remains challenging. Some residual confounding may persist, particularly through biological pathways that simultaneously influence both thyroid autoimmunity and cancer risk. Third, the relatively limited number of strong genetic instruments available for AIT may have constrained our ability to detect weaker but potentially meaningful causal relationships. This limited instrument strength could have reduced statistical power for certain cancer types, possibly resulting in false-negative findings. Future studies incorporating larger GWAS datasets may help address this limitation by identifying additional valid instruments. Fourth, our focus on genetic liability necessarily excluded consideration of important environmental modulators (e.g., iodine intake, radiation

exposure, and medications) and gene–environment interactions that may meaningfully influence cancer risk in the context of AIT/HT. The complex interplay between genetic predisposition and environmental triggers in both autoimmunity and carcinogenesis suggests that a more comprehensive model incorporating both factors would provide a more complete picture of these relationships. Despite these limitations, our study provides important insights into the intricate links between thyroid autoimmunity and cancer risk, while also highlighting key directions for future research.

5. Conclusion

Our analyses demonstrate that genetic predisposition to AIT/HT does not confer an increased risk for thyroid cancers, contradicting the long-held assumption that chronic thyroid inflammation directly promotes malignant transformation in thyroid tissue. This null association suggests that previously observed epidemiological links between AIT and thyroid cancer may primarily reflect detection bias or shared environmental risk factors, rather than causal biological mechanisms. These findings have immediate clinical implications, as they argue against intensive thyroid cancer surveillance strategies based solely on a patient's AIT/HT status, which could lead to overdiagnosis and unnecessary interventions.

Conversely, our study reveals that genetic liability to AIT/HT may serve as a novel risk factor for specific extra-thyroidal malignancies, most notably NHL. The observed causal association with NHL is consistent with established clinical observations of increased lymphoma risk in autoimmune populations. These findings significantly advance our understanding of cancer etiology by highlighting thyroid autoimmunity as a potential modulator of oncogenesis in specific non-thyroidal tissues. Future research should focus on elucidating the precise immunological mechanisms underlying these relationships. From a translational perspective, our results suggest that patients with AIT/HT might benefit from targeted surveillance for specific non-thyroidal malignancies, particularly in the presence of additional risk factors. This study also underscores the value of genetic approaches in disentangling complex disease relationships that are difficult to investigate using conventional epidemiological methods alone.

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Conflict of interest

The authors declare that they have no competing interests.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

All datasets generated during the present study are included in the article and/or the supplementary materials. Further inquiries can be directed to the corresponding authors.

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