

Mendelian randomization analysis provides insights into the relationship between inflammatory bowel disease and skin cancer

SAREM RASHID^{1,2}, DMITRII USOLTSEV³, SAMEER GUPTA⁴, MYKYTA ARTOMOV^{3,5*} and HENSIN TSAO^{1*}

¹Wellman Center for Photomedicine, Massachusetts General Hospital, Harvard Medical School, Boston, 02114 MA, USA;

²Boston University School of Medicine, Boston, 02118 MA, USA; ³Broad Institute, Cambridge, 02142 MA, USA;

⁴Massachusetts Eye and Ear, Boston, 02114 MA, USA; ⁵The Steve and Cindy Rasmussen Institute for Genomic Medicine, Nationwide Children's Hospital, Columbus, 43205 OH, USA

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Abstract. Limited and conflicting data have been available regarding the association between inflammatory bowel disease and skin cancer. It was hypothesized that inflammatory bowel diseases [Crohn's disease (CD) and ulcerative colitis (UC)] harbor a genetically increased risk of skin cancer [skin cutaneous melanoma (SKCM), basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] and performed two-sample mendelian randomization (MR) analysis using genome-wide association (GWAS) studies of European ancestry retrieved from FinnGen R8. The inverse variance weighted method was used to approximate MR effects. Sensitivity analyses including weighted median, MR-Egger and MR-pleiotropy residual sum and outlier were performed to estimate pleiotropy and heterogeneity *a priori*. MR results suggest a significant causal association between UC and SKCM, ($\beta=0.097$, $P=0.0138$) and UC and SCC ($\beta=0.171$, $P=0.0014$). These findings were then validated using summary-level GWAS from the UK Biobank and an independent meta-analysis which demonstrated a suggestive or causal genetic association between UC and SCC ($\beta=0.065$, $P=0.036$), UC and BCC ($\beta=0.056$, $P=0.002$), but not UC and SKCM ($\beta=0.02$,

$P=0.432$). Due to limited sample size for CD instruments, only 5 significant single nucleotide polymorphisms were found with no significant causal effects on skin cancer. These results provide evidence for a causal genetic association between UC and skin cancer through shared polymorphisms involving the IL-23/Th17 axis, which may inform preventative counseling and precision medicine in the future.

Introduction

The incidence of numerous multifactorial diseases, including skin cancer and inflammatory bowel diseases, has steadily increased worldwide over the past several decades (1-3). Previous studies have proposed an increased risk of both melanoma and non-melanoma skin cancers (NMSC) in patients with inflammatory bowel disease (IBD) (4-6). This association was previously considered to be a direct consequence of thiopurine therapy due to the increased generation of reactive oxygen species from 6-thioguanine (4,7). However, Lo *et al* (8) reported in their meta-analysis that patients with IBD demonstrate an increased risk of NMSC even when controlled for immunosuppressant use [Crohn's disease (CD) incidence rate ratio (IRR)=2.22; 95% confidence interval (CI): 1.41-3.48]; ulcerative colitis (UC) IRR=1.38; 95% CI: 1.12-1.71]. Genome-wide association studies (GWAS) have also identified numerous susceptibility loci associated with IBD, with some loci also implicated in cancer, but not skin cancer specifically (9). Although a clear biological explanation linking IBD with skin cancer has yet to be established, sustained cutaneous inflammation (10), immune suppression (11), and shared germline susceptibility are suspected to play a role (12).

While ultraviolet radiation (UVR)-induced mutagenesis remains to be the most well-established risk factor for skin cancer (13), emerging evidence suggests that neuro-immuno-endocrine mechanisms within the skin may contribute to skin cancer susceptibility (14-17). The neuro-immuno-endocrine functions of the skin involves a complex set of components and interactions spanning different organs, including the brain, gut and adrenal glands (14). Circulating immune cells, such as macrophages, lymphocytes and Langerhans cells, interact with cutaneous nerve

Correspondence to: Dr Hensin Tsao, Wellman Center for Photomedicine, Massachusetts General Hospital, Harvard Medical School, 55 Fruit St 148, Boston, 02114 MA, USA
E-mail: htsao@mgh.harvard.edu

Dr Mykyta Artomov, The Steve and Cindy Rasmussen Institute for Genomic Medicine, Nationwide Children's Hospital, 575 Children's Crossroad, Columbus, 43205 OH, USA
E-mail: mykyta.artomov@nationwidechildrens.org

*Contributed equally

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fibers to modulate host defense, inflammation and tissue repair (18). Neuropeptides released from nerve terminals may further modulate the function of cutaneous immune cells, while immune-derived mediators can influence neuronal activity, contributing to sensations such as itch and pain (19). UVR-induced modulation of cytokines such as TNF α , IL-1 and IL-6 drive pathways such as the central HPA axis to generate immunosuppressive effects (20).

Vitamin D signaling, particularly through the vitamin D receptor (VDR), plays a significant role in melanoma progression and management (21,22). The VDR is a nuclear receptor activated by 1,25-dihydroxyvitamin D3 (calcitriol), which influences various cellular processes including proliferation, differentiation and immune responses. High VDR expression in melanoma cells is associated with improved outcomes and reduced melanoma-related mortality (22). This is partly due to the inhibition of the Wnt/ β -catenin signaling pathway, which is known to promote melanoma progression (23). Despite increasing evidence unraveling the neuro-immuno-endocrine potential of the skin, current mechanisms remain to be poorly understood and are primarily derived from animal models and limited clinical studies.

Mendelian randomization (MR) is a powerful tool used to explore causal relationships between exposure traits and disease outcomes by utilizing genetic variants as proxies for the exposure of interest, thereby minimizing confounding and reverse causation (24). Over the past year, recent MR efforts for IBD and skin cancer have yielded mixed results, with some evidence to support causal effects for UC on NMSC in East Asian and European cohorts (25,26).

Given the growing availability of GWAS data and the need to clarify these associations, it was sought to determine whether there is a causal genetic relationship between IBD subtypes (CD and UC) and skin cancer (both melanoma and non-melanoma) using publicly available GWAS repositories. The present study aims to provide further insights into the potential shared genetic architecture between these conditions and to elucidate whether the observed associations are likely to be causal or a result of confounding factors.

Materials and methods

Instrument selection. Summary statistics were gathered and imputed against a Finnish-specific whole genome sequence backbone containing 20,175,454 variants. From 356,077 total controls, summary statistics were retrieved from FinnGen R8 for: CD (1,531 cases), UC (4,857 cases), SKCM (2,993 cases), BCC (18,982 cases) and SCC (251 cases). Lead significant single nucleotide polymorphisms (SNPs) with genome-wide significance level ($P < 5 \times 10^{-8}$) were then selected and linkage disequilibrium pruning (r^2 threshold=0.001, clumping window=10 Kb) was employed to distinguish highly correlated SNPs. Ethics approval was not required for the present study because no individual-level data were used in summary statistics.

To assess the robustness of the present findings, skin cancer GWAS summary statistics for significant MR associations were also retrieved from the UK Biobank (UKBB) consortium representing self-reported and code-verified cases of SKCM (3,322 cases; 417,151 controls), BCC (7,402 cases; 286,892

controls) and SCC (7,402 cases; 286,892 controls) as part of a secondary study. Summary statistics for UC in the secondary study were retrieved from a 2015 meta-analysis of European ancestry containing 6,968 cases and 20,464 controls (9).

Data preparation. Data preparation and MR analysis was performed using the TwoSampleMR (27) package (Version 0.5.6) within R. Instrumental variables were harmonized to matching effect alleles with palindromic SNPs excluded. The fixed-effect inverse variance weighted (IVW) method was selected to approximate exposure effects on outcome. The IVW method assumes all genetic variants are instrumental variables, and is a common estimator used in two-sample MR (28). MR causal effects (β) were considered significant at a Bonferroni-corrected P-value $0.05/3 = 0.017$, with P-values > 0.017 , with $P < 0.05$ considered as a suggestive association.

Sensitivity analyses. Sensitivity analysis were used in the present study to assess whether our results violated key MR assumptions (29). Importantly, genetic instruments should not be associated with potential confounding variables. The MR-EGGER intercept test was used to assess whether the fixed-effect IVW estimate is biased by the presence of directional pleiotropy. To further check for the presence of directional pleiotropy, MR pleiotropy residual sum and outlier (MR-PRESSO) estimates were subsequently incorporated into our sensitivity analysis. For this test, the global test P-value detects for the presence of horizontal pleiotropy in the IVW estimate. If horizontal pleiotropy was detected in the first step, then MR-PRESSO corrected the raw IVW estimate to mitigate outlier effects. Heterogeneity calculations were also performed to assess the stability and consistency of SNP effects across analyses.

Results

Genetic associations for IBD and three major types of skin cancer [cutaneous melanoma (SKCM), basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] were retrieved from FinnGen Release 8 (R8) and subjected to two-sample MR. There were a total of 371 significantly-associated variants for CD and 3,193 variants for UC available for MR. An overview for genetic instrument selection is shown in Fig. 1.

There were 26 significant SNPs associated with UC as an exposure post-harmonization (Fig. 2). Fixed-effect IVW regression showed significant causal effects for SKCM ($\beta = 0.097$, $se = 0.039$, $P = 0.0138$) and SCC ($\beta = 0.171$, $se = 0.054$, $P = 0.0014$), but not BCC ($\beta = 0.056$, $se = 0.030$, $P = 0.0610$) (Table SI). A causal association was also observed using MR-EGGER regression, although MR estimates were found to lack significance. Using Cochran's Q test, the presence of heterogeneity was observed for SKCM ($Q = 27.043$, $P = 0.302$), which was shown to increase for SCC ($Q = 51.914$, $P = 8.03 \times 10^{-4}$) (Table I). Due to presence of heterogeneity, a random-effect IVW analysis was performed and showed a consistent association for SKCM ($\beta = 0.0862$, $P = 0.0157$) and SCC ($OR = 0.174$, $P = 6.57 \times 10^{-4}$). For SKCM, the MR-EGGER intercept test showed presence of directional pleiotropy (intercept = -0.0058, $P < 2.2 \times 10^{-16}$) with no outlier correction using MR-PRESSO. For SCC, there was also presence of directional

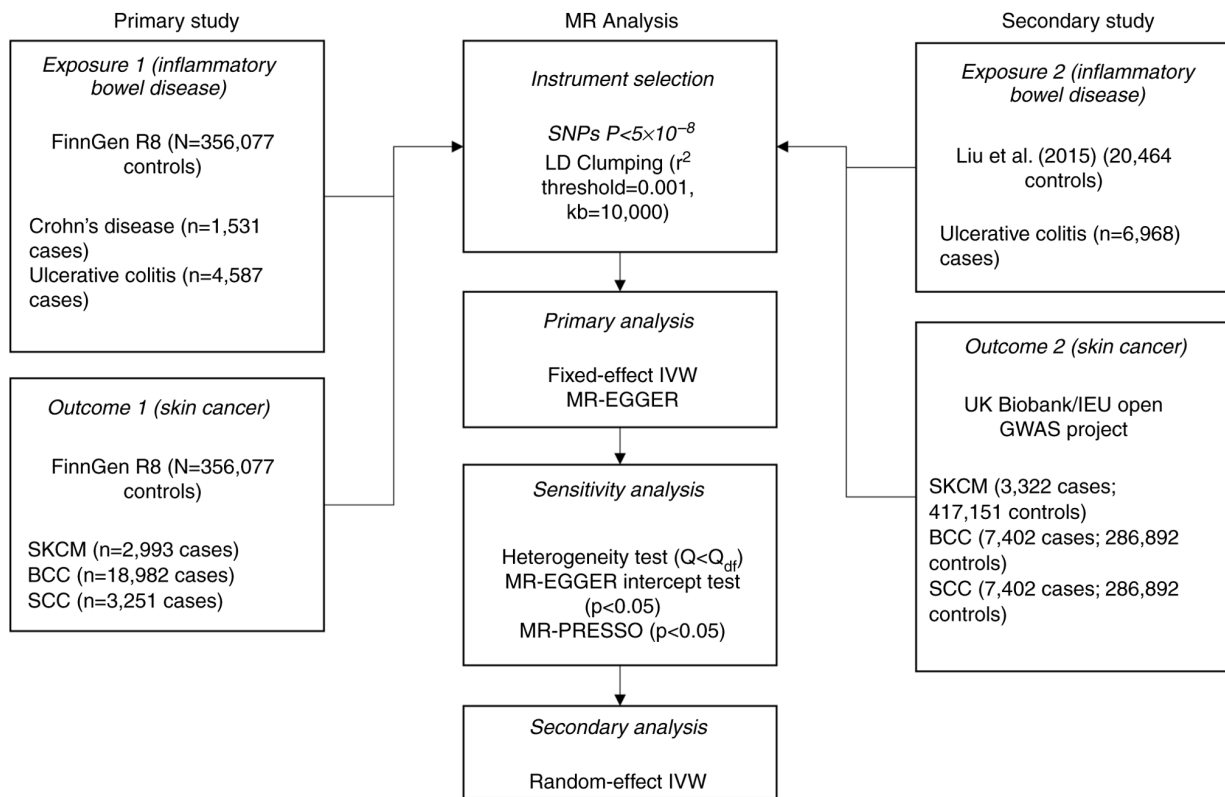


Figure 1. Flowchart of data collection, processing and analysis for the present study. The primary study was conducted using IVs selected from FinnGen R8, whereas the secondary study was conducted using IVs sourced from a 2015 meta-analysis (9) and UKBB for exposure and outcome IVs, respectively. IVs, instrumental variables; SKCM, skin cutaneous melanoma; BCC, basal cell carcinoma; SCC, squamous cell carcinoma; GWAS, genome-wide association studies; MR, mendelian randomization; IVW, inverse variance weighted.

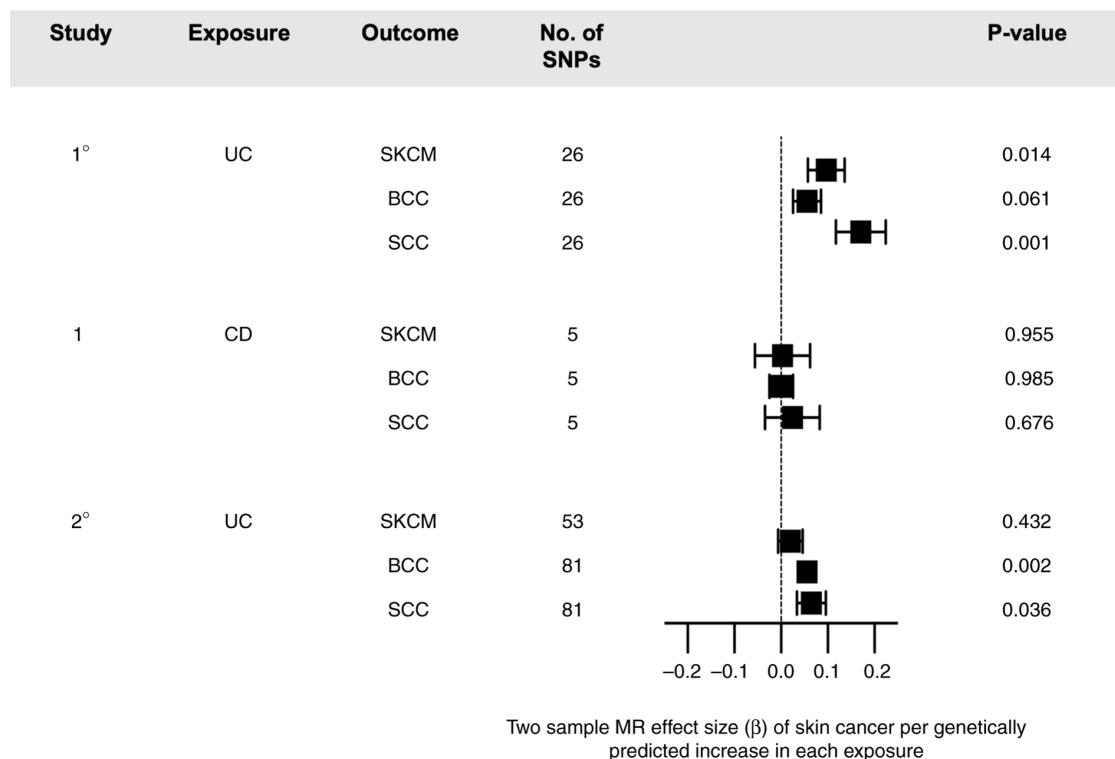


Figure 2. Forest plot of two-sample MR analysis for inflammatory bowel disease (CD and UC) and skin cancer (SKCM, BCC and SCC) using fixed-effect IVW regression. Primary study (1°) instrument variables are derived from FinnGen R8. Secondary study (2°) instrument variables are sourced from Liu *et al* (9) and the UK Biobank for exposure and outcome, respectively. Black squares represent the effect size (β) estimates for each association and error bars indicate standard error. MD, mendelian randomization; CD, Crohn's disease; UC, ulcerative colitis; SKCM, skin cutaneous melanoma; BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

Table I. Results of heterogeneity testing and sensitivity analyses for primary study genetic instruments.

Exposure	Outcome	Q	Q dF	Q P-value	MR EGGER			MR PRESSO	
					Intercept (SE)	r ²	P-value	Global test P-value	Outlier correction
Ulcerative colitis	SKCM	27.043	25	0.302	-0.0058 (0.002)	0.03	<2.2x10 ⁻¹⁶	0.332	No
	BCC	82.423	25	2.49x10 ⁻⁸	-0.034 (0.002)	0.14	<2.2x10 ⁻¹⁶	<0.001	Yes
	SCC	51.914	25	8.03x10 ⁻⁴	-0.068 (0.003)	0.19	<2.2x10 ⁻¹⁶	<0.001	Yes
Crohn's disease	SKCM	0.700	4	0.873	0.0041 (0.006)	0.02	8.93x10 ⁻³	0.45	No
	BCC	1.402	4	0.705	-0.013 (0.005)	0.003	0.297	0.779	No
	SCC	0.273	4	0.965	-0.054 (0.007)	0.05	3.62x10 ⁻⁵	0.874	No

SKCM, skin cutaneous melanoma; BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

pleiotropy (intercept=-0.068, $P<2.2\times 10^{-16}$) with outlier correction (OR=0.0392, $P=0.102$) showing no significant association.

Using CD as an exposure, only 5 significant SNPs were included post-harmonization for MR analysis. MR using IVW regression demonstrated no significant causal effects for SKCM (beta=0.003, se=0.059, $P=0.955$), BCC (beta=4.82x10⁻⁴, se=2.54x10⁻², $P=0.985$), or SCC (beta=0.024, se=0.058, $P=0.676$). No heterogeneity was found using Cochran's Q test. Directional pleiotropy was again detected for SKCM (intercept=0.004, $P=8.93\times 10^{-3}$) and SCC (intercept=-0.054, $P=3.62\times 10^{-5}$), with no outlier correction using MR-PRESSO.

To test the reproducibility of causal effects observed for UC, GWAS summary statistics from Liu *et al* (9) and the UK Biobank (Fig. 1) were utilized for a secondary study. A total of 83 significant SNPs were found post-harmonization for SKCM, and 81 significant SNPs found for both BCC and SCC. MR analysis demonstrated suggestive or significant causal effects between UC and SCC (beta=0.065, se=0.031, $P=0.036$) and UC and BCC (beta=0.056, se=0.018, $P=0.002$), but not UC and SKCM (beta=0.020, se=0.026, $P=0.432$).

Discussion

The current analysis indicates causal effects for UC on SCC, which is supported by a recent meta-GWAS East Asian and European ancestries (25). Secondary analysis using datasets from the UK Biobank replicated the significant associations for UC and SCC, providing additional evidence for this relationship using European cohorts. Utilization of the FinnGen R8 dataset in the present study offered a high prevalence of cases relative to total population compared with other publicly available datasets. Moreover, imputation with Finnish-specific panels has also been shown to demonstrate high accuracy for low-frequency variants (30). The influence of confounding bias was controlled for using strict selection of instrumental variables and *a priori* sensitivity analyses. Sensitivity testing showed moderate heterogeneity with possible pleiotropy for the UC and skin cancer associations. Ultimately, these findings suggest that select genetic variants may influence skin cancer through pathways unrelated to UC, although outlier correction was applied to account for the observed pleiotropy.

There are a few noteworthy observations from the 26 UC-associated SNPs used for MR (Table SII). First, rs3024493, proximal to interleukin 10 (IL-10), has been linked to the development of IBD in genetic studies (31,32). IL-10 is an important immunoregulator of mucosal immunity which acts by inhibiting proinflammatory cytokines (IL-1 β , TNF- α and IL-6), Th2 cell-derived cytokines (IL-4 and IL-5), and chemokines (MIP-1 α and interleukin-8), while increasing synthesis of several anti-inflammatory proteins (33). In patients with melanoma, rs3024493 has been linked with downregulation of IL-10 secretion in CD4⁺ T cells. Multivariate analyses have demonstrated decreased melanoma overall survival [hazard ratio (HR): 4.73; 95% CI: 1.68-13.29] for minor allele homozygotes (TT) compared with major allele homozygotes (GG), although interestingly show improved overall survival (HR: 0.58, 95% CI: 0.39-0.86) in heterozygotes (GT). Conversely, increased production of IL-10 in keratinocyte carcinomas has been hypothesized as a mechanism for evading local T cell-mediated immune responses (34). This may suggest that the

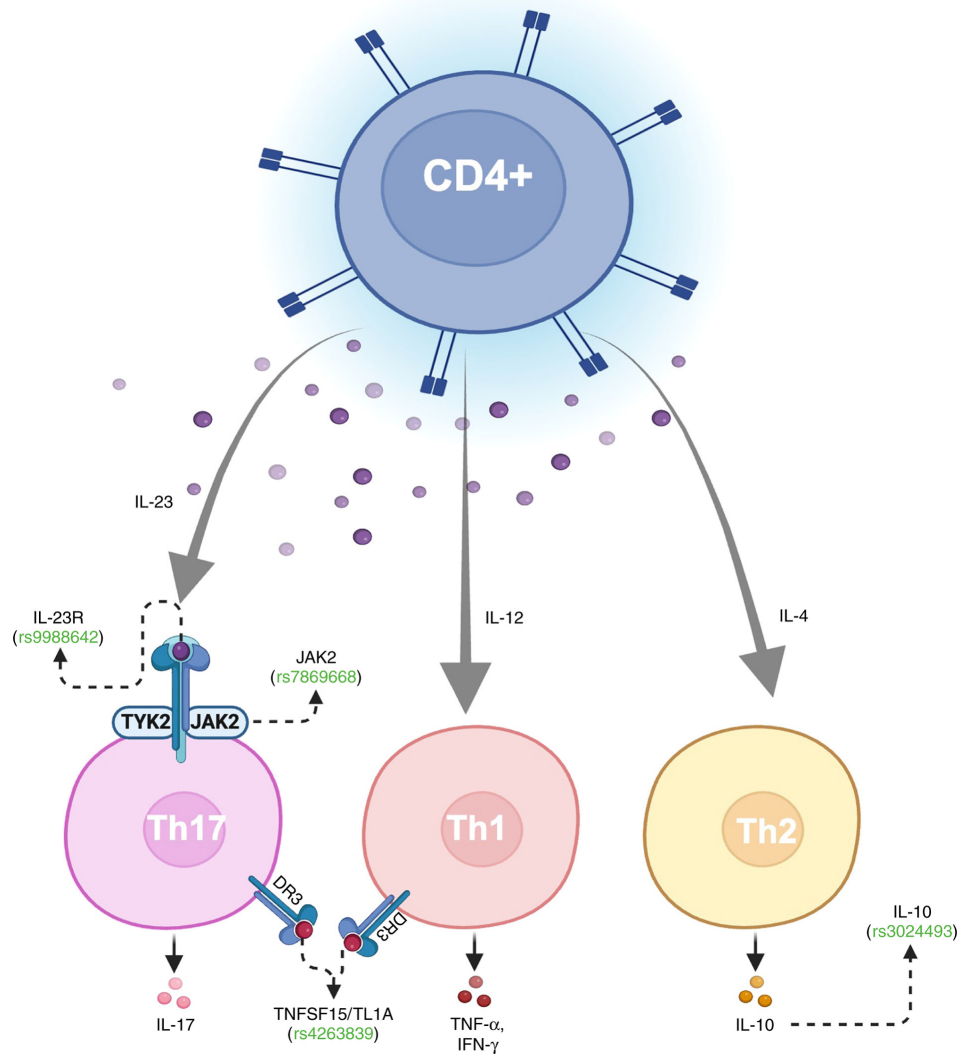


Figure 3. IL-23 promotes the differentiation of naïve CD4⁺ T cells into IL-17-producing Th17 cells through the TYK2-JAK2 signaling pathway, influenced by genetic variants rs9888642 and rs7869668. Th17 cells secrete IL-17, contributing to inflammatory responses. Similarly, IL-12 drives Th1 differentiation, leading to TNF- α and IFN- γ production, with rs4263839 in TNFSF15/TL1A associated with Th1 regulation. IL-4 induces Th2 differentiation, promoting IL-10 secretion, with rs3024403 linked to this pathway. Figure created using BioRender (<https://www.biorender.com/>).

regulatory function of IL-10 extends to skin immunity and cancer progression. Given that UV radiation modulates cytokine expression, including IL-10, it is plausible that chronic UV exposure may provide a potential link between chronic inflammation and immune escape mechanisms in skin cancer (35).

More broadly, the IL-23/Th-17 axis for inflammation has been implicated in both IBD (36) and skin cancers (37,38). When bound to IL-23R (rs9988642), IL-23 activates JAK2 (rs7869668) to facilitate differentiation of naïve CD4⁺ T-cells into IL-17-secreting Th17 cells (Fig. 3). This differentiation process establishes a pro-inflammatory microenvironment which favors tumorigenesis. TL1A (rs4263839) interacts with DR3 to synergistically increase the production of IL-17 and other pro-inflammatory cytokine as observed in CD (39,40). IL-17 then acts to promote infiltration of myeloid-derived suppressor cells and activate the STAT3 signaling pathway, which has been canonically associated with increased tumor cell proliferation, survival, and angiogenesis (41-43). Together, these interactions collectively reinforce the IL-23/Th17 axis as a potential driver of inflammation-mediated tumorigenesis.

The skin and gut function as the two largest immune systems in the human body, each employing distinct yet overlapping biological mechanisms (44). Dysbiosis in the gut microbiota drives biological crosstalk in what is known as the skin-gut axis, in which cell trafficking between the skin and gut promotes frequent comorbidity of inflammatory diseases (45). Recent findings suggest that gut-derived metabolites (for example, short-chain fatty acids, bile acids and vitamins) influence skin barrier function (46-48), while skin-derived inflammatory mediators may exacerbate gut inflammation (49,50). Furthermore, immune cell trafficking between the gut and skin is increasingly recognized as a mechanism for disease spread (45). Aberrant migration of gut-educated T cells has been implicated in both cutaneous and gastrointestinal inflammation (51,52), even extending to other inflammatory diseases such as ankylosing spondylitis and primary sclerosing cholangitis (52,53).

While gut and skin leukocytes are typically directed to their respective tissues, the presence of inflammation may alter homing patterns. For instance, intestinal T cells may acquire skin-homing

characteristics during chronic gut inflammation, leading to secondary cutaneous disease (54). Conversely, skin-resident memory T cells may enter circulation and contribute to systemic inflammation, as observed in graft-vs.-host disease (55). These insights also have therapeutic implications for modulating gut-skin immune cell trafficking. For example, the use of vedolizumab, a gut-selective integrin blocker used in IBD, has been hypothesized to modulate binding of $\alpha_4\beta_7$ -MAdCAM1 for gut access and subsequent skin entry (56).

The present study has several important limitations. First, the limited number of CD cases (1,531 in FinnGen R8) resulted in the identification of only five genome-wide significant SNPs available for MR analysis post-harmonization. This small number of instruments significantly weakened the strength of the genetic proxies for CD, therefore increasing the likelihood of weak instrument bias. As a result, no significant causal associations were observed between CD and skin cancer outcomes in our MR analyses. Additionally, while the use of Finnish-specific GWAS data enhances variant detection, the findings may not be fully generalizable to other populations with more diverse genetic backgrounds. Finally, the presence of pleiotropy, as suggested by the MR-EGGER intercept tests, indicates that some genetic variants might influence skin cancer risk through mechanisms that are independent of IBD.

Overall, the present study demonstrates a causal genetic association between UC and SCC in European cohorts distinct from biologic-induced skin cancer in previous literature. The demonstrated genetic associations may provide meaningful implications for clinical practice, particularly in terms of risk stratification, preventative counseling and surveillance strategies for patients with IBD. While UV exposure remains the predominant risk factor for SCC, IBD-related immune dysregulation may create a permissive environment for carcinogenesis. Patients with UC, particularly those with long-standing disease, may benefit from personalized preventative strategies, including education on sun safety, regular dermatologic screenings, and early intervention measures. Further investigation of the IL-23/Th17 axis in UC-associated SCC may elucidate underlying disease mechanisms and inform the development of new targeted therapeutic strategies.

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Availability of data and materials

The data generated in the present study may be found at the following URLs: FinnGen (<https://www.finnngen.fi/en>), UK Biobank (<https://www.ukbiobank.ac.uk/>), and the IEU Open GWAS Project (<https://gwas.mrcieu.ac.uk/>).

Authors' contributions

SR, DU, SG, MA and HT conceptualized and designed the study, conducted formal analysis, prepared the original draft,

and wrote, reviewed and edited the manuscript. SR, MA and HT curated data. HT acquired funding. All authors read and approved the final version of the manuscript. SR and HT confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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